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Mortality and Short-term Morbidities in Very Preterm Infants in Tertiary Care Center: One-year Observational Study

Mortalitet i kratkoročni morbiditeti kod vrlo prijevremeno rođene djece u tercijarnom zdravstvenom centru: jednogodišnja opservaciona studija

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ABSTRACT

Introduction:preterm birth is a leading cause of neonatal morbidity and mortality. Despite advances in neonatal care, extremely and very-preterm infants remain at high risk for complications. Outcomes vary regionally, with limited data from Bosnia and Herzegovina. Aim:to analyze survival and short-term outcomes in preterm infants at the Clinical Center University of Sarajevo over one year period.Materials and methods:aretrospective cohort study analyzing outcomes of preterm infants (gestational ages-GA between 24+0 and 31+6 weeks), delivered at the Clinical Center University of Sarajevo from 1 January 2023 to 31 December 2023, and admitted to the Neonatal Intensive Care Unit (NICU). Outcome criteria was mortality rate and short-term morbidities that included: bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) and survival free of major complications.Results:overall, survival rate was 75.8%, with survival rate of 56.7% in extremely low GA group and 85.2% in very low GA group.Major short-term outcomes were observed in 20% of the overall cohort, with 47% in the extremely preterm group and 6.6% in the very preterm group. Overall, the incidence proportion for BPD, severe IVH, severe ROP and severe NEC was 1.1%, 15%, 5.5% and 1.1%, respectively. Survival free of major complications was observed in 67% of all neonates (33% in the extremely preterm group and 84% in the very preterm group). Low gestational age (GA) and prolonged rupture of membranes (PROM) were significant risk predictors for death or adverse short-term outcomes.Conclusion:this study highlights the impact of gestational age and prolonged rupture of membranes on mortality and adverse short-term outcomes in very preterm and extremely preterm infants in the NICU at the Clinical Center University of Sarajevo. Further research on maternal risk factors and long-term outcomes is needed to improve preterm infant care in upper-middle-income countries.Despite comparable composite outcome rates to high-income countries, higher mortality was observed, particularly in the extremely preterm infants.

Keywords: preterm infants, mortality, short-termoutcomes, morbidity

SAŽETAK

Uvod: prijevremeni porođaj predstavlja vodeći uzrok neo natalnog morbiditeta i mortaliteta. Uprkos napretku u neonatalnoj njezi, ekstremno i vrlo prijevremeno rođene djece i dalje su izložene visokom riziku za komplikacije. Ishodi variraju regionalno, a podaci iz Bosne i Hercegovine su ograničeni. Cilj: analizirati preživljavanje i kratkoročne ishode prijevremeno rođene djece u Kliničkom centru Univerziteta u Sarajevu tokom jednogodišnjeg perioda. Materijali i metode: retrospektivna kohortna studija analizirala je ishode prijevremeno rođene djece (gestacijska dob između 24+0 i 31+6 sedmica), koja su rođena u Kliničkom centru Univerziteta u Sarajevu od 1. januara 2023. do 31. decembra 2023. godine i primljena na Odjel neonatalne intenzivne njege (NICU). Ishodi su uključivali stopu mortaliteta i kratkoročne morbiditete kao što su: bronho-pulmonalna displazija (BPD), intraventrikularno krvarenje (IVH), nekrotizirajući enterokolitis (NEC) i retinopatija prematuriteta (ROP), kao i preživljavanje bez većih komplikacija. Rezultati: ukupna stopa preživljavanja iznosila je 75,8%, s preživljavanjem od 56,7% u grupi ekstremno prijevremeno rođenih beba i 85,2% u grupi vrlo prijevremeno rođenih beba. Veći kratkoročni ishodi zabilježeni su kod 20% ukupne kohorte, sa 47% u grupi ekstremno prijevremenih i 6,6% u grupi vrlo prijevremenih beba. Ukupna incidenca za BPD, teško IVH, teško ROP i teško NEC bila je 1,1%, 15%, 5,5% i 1,1%, respektivno. Preživljavanje bez većih komplikacija zabilježeno je kod 67% svih novorođenčadi (33% u grupi ekstremno prijevremenih i 84% u grupi vrlo prijevremenih beba). Niska gestacijska dob (GA) i produžena ruptura membrana (PROM) bili su značajni prediktori rizika za smrt ili nepovoljne kratkoročne ishode. Zaključak: ova studija naglašava uticaj gestacijske dobi i produžene rupture membrana na mortalitet i nepovoljne kratkoročne ishode kod vrlo i ekstremno prijevremeno rođenih beba u NICU Kliničkog centra Univerziteta u Sarajevu. Potrebna su dodatna istraživanja o faktorima rizika majki i dugoročnim ishodima kako bi se unaprijedila njega prijevremeno rođene djece u zemljama s višim srednjim prihodima. Uprkos usporedivim stopama kompozitnih ishoda s visokorazvijenim zemljama, uočen je veći mortalitet, posebno kod ekstremno prijevremenih beba.

Ključne riječi: prijevremeno rođena djeca, mortalitet, kratkoročni ishodi, morbiditet

INTRODUCTION

Preterm birth, defined as delivery before 37 weeks of gestation, remains a leading cause of neonatal morbidity and mortality worldwide. Among preterm births, very preterm (28+0 to 31+6 weeks) and extremely preterm (24+0 to 27+6 weeks) deliveries pose significant challenges to neonatal care due to the increased risk of life-threatening complications and long-term developmental impairments (1). Advances in neonatal intensive care have improved survival rates for these vulnerable populations, yet the burden of major short-term morbidities such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) remains substantial. These outcomes underscore the need for continued research to refine management strategies and improve care (2). The outcomes for very preterm and extremely preterm infants vary significantly based on regional and institutional care practices, with tertiary care centers often being uniquely positioned to provide specialized treatment (3). The Neonatal Intensive Care Unit (NICU) at Clinical Center University of Sarajevo represents one such center, serving as a referral unit for high-risk deliveries and providing critical interventions for preterm infants. In Bosnia and Herzegovina, which is an upper middle income country according to the World Bank(4), data on outcomes of very preterm and extremely preterm infants are limited. Additionally, evaluating the impact of factors such as antenatal care, use of steroids, and pregnancy characteristics on neonatal outcomes can guide clinical decision-making and inform public health initiatives (3).

This study aims to analyze the outcomes of very preterm and extremely preterm infants delivered at the Clinical Center University of Sarajevo over a one-year period. By examining survival rates and the incidence of major short-term morbidities, this research provides a comprehensive overview of neonatal outcomes in a tertiary care setting, helping to contextualize these outcomes within broader regional and global data.

AIM

The aim of this study was to analyze survival and short-term outcomes in preterm infants at the Clinical Center University of Sarajevo over one year period.

MATERIALS AND METHODS

This retrospective cohort study included all very preterm and extremely preterm infants, with gestational ages between 24+0 and 31+6 weeks, delivered at the Clinical Center University of Sarajevo from 1 January 2023 to 31 December 2023, and admitted to the Neonatal Intensive Care Unit (NICU).

The exclusion criteria were stillbirths, infants who died in the delivery roomand infants transferred from other medical centers to the Clinical Center University of Sarajevo NICU for further care.

Data were obtained from medical histories and discharge summaries of each infant. The following variables were documented: gestational age, birth weight, gender, mode of conception (natural or in-vitro fertilization IVF), prolonged rupture of membranes (PROM), use of antenatal corticosteroids, use of antibiotics prior to delivery, pregnancy type (single or multiple), mode of delivery (vaginal or cesarian), Apgar scores, survival status and major short-term outcomes: BPD, IVH, ROP and NEC.

Definitions followed the World Health Organization (WHO) guidelines, categorizing infants with very low gestational age(VLGA) as those born between 28+0 and 31+6 weeks of gestation, and extremely low gestational age (ELGA) as those born between 23+0 and 27+6 weeks. Birth weights below 1500 g defined very low birth weight (VLBW) infants, while those under 1000 g were classified as extremely low birth weight (ELBW) infants (5). A complete course of antenatal steroids was defined as two doses administered 24 hours apart, with the final dose given more than 24 hours before delivery.

Overall mortality was defined as all deaths occurring after birth until discharge from the hospital that occurred on the NICU. BPD was diagnosed and defined as present amonginfants requiring oxygen supplementation at discharge or at 36 weeks corrected gestational age (6). NEC diagnosis followed Bell's criteria, with severe NEC requiring surgical intervention (7). IVH classification was based on Papile LA, et al., with severe IVH defined as Grades III or IV (8) . ROP severity was determined per the international classification, with Grades III toV considered severe (9).

Major short-term outcomes were defined as the presence of any of the following morbidities: BPD, severe NEC, severe IVH, and/or severe ROP. Survival without any of these four major morbidities was categorized as survival without major complications.

Statistical analysis

Statistical analysis was conducted in R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive summaries are reported as mean (±SD) or median [Q1 – Q3] for numerical and ordinal variables, as applicable. Dichotomous and categorical variables are reported as absolute (n) and relative (%) frequencies.

Quantitative variables following normal distribution were tested for differences in means with Student's t-test, and quantitative variables violating the presumptions of normal distribution, as well as ordinal variables, were tested for difference between groups with Wilcoxon rank-sum test. In case of categorical variables, differences in frequency distributions were tested through Pearson's 2 test, or Fisher's exact test when number of observations in category was ≤5. Quantitative variables were assessed for normality via histograms, QQ plots and Shapiro-Wilk's test.

Logistic regression was used in univariable and multivariable analysis to build models and identify magnitude and significance of associations. Along with clinical knowledge pertaining to clinically important predictor variables, model selection following backward stepwise regression procedure based on AIC value was used to select the best-fitting and explainable model. In logistic regression, survival free of major complications was treated as no event, while death or any of adverse short-term outcomes (severe IVH, severe ROP, severe NEC, or BPD) was treated as an event.

Ethics

The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

A total of 91 neonates were included in the study (30 in the ELGS group and 61 in VLGA group), with a mean birth weight of 1,229 (± 332) grams and mean gestational age (GA) of 29 (± 2.0) weeks. 7 neonates were excluded from the study based on the exclusion criteria. Neonate characteristics are summarized in Table 1 and stratified by GA.

There was no significant difference in gender distribution overall or between the GA groups. Birth weight and APGAR score in both 1st and 5th minute were markedly lower in the extremely preterm group ($p<0.001$). Overall, caesarean delivery was more common (58.2%) with significant difference in mode of delivery between the groups (40% for ELGA vs. 67.2% forVLGA) ($p=0.013$).

Multiple pregnancies were more frequent among very preterm neonates (32.8%) than among extremely preterm neonates (13.3%) (p=0.048).

IVF pregnancy (p=0.10), PROM (p=0.079), and the use of antenatal corticosteroids (p=0.6), showed no significant differences between the groups. Among those receiving antenatal corticosteroids, a complete course was administered in 87.5% of cases, with no notable difference between extremely preterm (91.7%) and very preterm (85.7%) neonates (p>0.9). Similarly, the administration of antibiotics prior to delivery was comparable between groups (p=0.3).

Table 1 **Neonate characteristics, stratified by gestational age.**

		Gestational age		
Characteristic	**Overall N = 91 [1]**	**Extremely preterm (<28 weeks) N=30 [1]**	**Very preterm (28-32 weeks) N=61 [1]**	**p-value**
Gender				0.3 [2]
Female	43 (47.3%)	12 (40.0%)	31 (50.8%)	
Male	48 (52.7%)	18 (60.0%)	30 (49.2%)	
Mortality	22 (24.2%)	13 (43.3%)	9 (14.8%)	**0.003 [2]**
APGAR 1st minute	7 [4–8]	4 [3–6]	7 [6–8]	**<0.001 [3]**
APGAR 5th minute	8 [6–9]	6 [4–7]	8 [7–9]	**<0.001 [3]**
Birthweight (grams)	1,229 (±332)	964 (±256)	1,359 (±285)	**<0.001 [3]**
Mode of delivery				**0.013 [2]**
Vaginal	38 (41.8%)	18 (60.0%)	20 (32.8%)	
Caesarean	53 (58.2%)	12 (40.0%)	41 (67.2%)	
Pregnancy type				**0.048 [2]**
Single	67 (73.6%)	26 (86.7%)	41 (67.2%)	
Multiple	24 (26.4%)	4 (13.3%)	20 (32.8%)	
IVF pregnancy	12 (13.2%)	1 (3.3%)	11 (18.0%)	0.10 [4]
Prolonged rupture of membrane	23 (25.3%)	11 (36.7%)	12 (19.7%)	0.079 [2]
Antenatal corticosteroids	40 (44.0%)	12 (40.0%)	28 (45.9%)	0.6 [2]
Complete course of antenatal corticosteroids	35/40 (87.5%)	11/12 (91.7%)	24/28 (85.7%)	>0.9 [4]
Antibiotics prior to delivery	19 (20.9%)	8 (26.7%)	11 (18.0%)	0.3 [2]

[1] n (%); Median [Q1–Q3]; Mean (±SD); n/N Non-missing (%)
[2] Pearson's Chi-squared test
[3] Wilcoxon rank sum test
[4] Fisher's exact test

Mortality and short-term outcomes

Overall, 22 (24.2%) infants died. For ELGA infants, mortality rate was 43.3% and for VLGA infants it was 14.8% (Table 1).

Major short-term outcomes were more common in extremely preterm (<28 weeks) compared to very preterm (28–32 weeks) neonates (Table 2). Adverse short-term outcomes were observed in 20% of the overall cohort, with 47% in the extremely preterm group and 6.6% in the very preterm group. Overall, the incidence proportion for BPD was 1.1% (only in the VLGA group, 1.6%), for severe IVH 15% (33% in ELGA vs. 6.6% in VLGA group), for severe ROP 5.5% (only in the ELGA group, 17%) and for severe NEC 1.1% (only in the VLGA group, 1.6%) (Table 2).

Survival with an adverse short-term outcome was noted in 8.8% of neonates overall, with 23% in the extremely preterm group and 1.6% in the very preterm group. The composite outcome of death or adverse short-term outcomes was recorded in 33% of neonates, with 67% in the extremely preterm group and 16% in the very preterm group.

Survival free of major complications was observed in 67% of all premature neonates. This occurred in 33% of the extremely preterm group and 84% of the very preterm group. Sepsis was recorded in 25% of all premature infants, and its occurrence was 33% in ELGA group vs 25% in VLGA group.

Table 2 **Short-term outcomes of extremely low and very low GA infants.**

Characteristic	Overall N = 91 [1]	Prematurity	
		Extremely preterm (<28 weeks) N=30 [1]	Very preterm (28-32 weeks) N=61 [1]
Survival outcome			
Major short -term outcome(s)	18 (20%)	14 (47%)	4 (6.6%)
Severe IVH	14 (15%)	10 (33%)	4 (6.6%)
Severe ROP	5 (5.5%)	5 (17%)	0 (0%)
Severe NEC	1 (1.1%)	0 (0%)	1 (1.6%)
BPD	1 (1.1%)	0 (0%)	1 (1.6%)
Death or adverse short -term outcome	30 (33%)	20 (67%)	10 (16%)
Alive with adverse short -term outcome	8 (8.8%)	7 (23%)	1 (1.6%)
Survival free of major complications	61 (67%)	10 (33%)	51 (84%)
Sepsis	25 (27%)	10 (33%)	15 (25%)

[1] n (%)
Severe IVH – Intraventricular hemorrhage grade III or IV; Severe ROP – Retinopathy of prematurity (Grade III, IV and V);
Severe NEC– Necrotizing enterocolitis mandating surgical intervention,
BPD – Bronchopulmonary dysplasia Major short-term outcome (BPD, severe IVH, severe ROP, or severe NEC);
Survival free of major complications (survival without BPD, severe IVH, severe ROP, and severe NEC)

In the univariable regression analysis, low GA, low birth weight, lower 5th minute APGAR score, cesarian delivery and multiple births were significantly associated withdeath or major short-term outcome (Table 3). In the multivariable regression model, several associations from the univariable analysis were re-evaluated after adjusting for potential confounders. Low GA remained a strong risk predictor, with a much stronger OR of 4.37 (95% CI: 2.08–11.5) per one-week decrement.

In contrast, low birth weight, APGAR score, mode of delivery and pregnancy type showed diminished effects after adjustment, suggesting that effectswere confounded by other variables in the model. The effect of PROM stood out significantly in the multivariable model, with an OR of 29.4 (95% CI: 3.73–379), indicating a strong association with adverse outcomes independent of other variables. Male gender, although not statistically significant, showed an OR of 3.98 (95% CI: 0.89–22.1), indicating an association toward higher risk in the multivariable model (Table 3).

Table 3 **Univariable and multivariable association between predictors and death or short-term complications (IVH≥3, ROP≥3, Severe NEC, or BPD) in preterm infants (under 32 weeks of gestational age).**

	Univariable			Multivariable		
Characteristic	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
Gender						
Female	—	—		—	—	
Male	1.76	0.73-4.32	0.2	3.98	0.89-22.1	0.085
APGAR in 5th minute (one point decrement)	1.42	1.13-1.83	**0.004**	0.69	0.37-1.17	0.2
Gestational age (one -week decrement)	2.31	1.70-3.39	**<0.001**	4.37	2.08-11.5	**<0.001**
Birthweight (100 -gram decrement)	1.64	1.34-2.10	**<0.001**	1.03	0.76-1.42	0.8
Mode of delivery						
Vaginal	—	—		—	—	
Cesarean	2.49	1.03-6.20	**0.046**	0.46	0.09-2.10	0.3
Pregnancy type						
Single	—	—		—	—	
Multiple	7.90	2.09-51.8	**0.008**	0.85	0.07-12.4	0.9
IVF pregnancy	6.38	1.15-120	0.083			
Prolonged rupture of membrane	2.94	0.97-11.0	0.074	29.4	3.73-379	**0.004**
Complete course of antenatal corticosteroids	1.12	0.46-2.82	0.8	0.93	0.18-4.89	>0.9
Antibiotics prior to delivery	0.80	0.28-2.41	0.7			

[1] OR = Odds Ratio, CI = Confidence Interval

DISCUSSION

This study analyzed mortality and short-term morbidities in very preterm and extremely preterm infants admitted to the NICU of the Clinical Center University of Sarajevo.

In this study,the overall survival rate was 75.8%, with 56.7% for extremely premature infants and 85.2% for very premature infants. Available studies of the outcomes of preterm infants report varying data on survival, especially regarding the extremely preterm group ranging from 35-70%, and from 59-81% for those at 25 weeks of gestation (2).

The overall mortality rate of 24.2% in our study is comparable to the 22% mortality rate reported in aprospective multicenter study by the Turkish Neonatal Society (10). Limited data is available on mortality rates of preterm infants in other upper-middle-income countries in the region, though our observed rate is lower than the 30.5% mortality reported in a Croatian study (11). However, it remains significantly higher than mortality rates in high-income countries, where the overall rate before discharge is around 10% (ranging from 5% in Japan to 17% in Spain) (12). This indicates that significant challenges persist in reducing the burden of morbidities in preterm infants and are dependent on regional care practices and access to advanced medical interventions (12-14).

The composite outcome rate was 33% which is consistent with high-income countries where it varied from 26% to 42% between countries (12). Furthermore, survival without major complications was 67% in all of the cohort, a finding comparable to the 79% reported in Austrian preterm populations and higher than the 48% reported in Turkish preterm population (15). However, survival free of major complications in the extremely preterm infants was 33%, compared to Austrian study in which it was 51.9% (15).

In our study, sepsis was observed in 27% of all preterm infants, with a higher occurrence in the ELGA group (33%) compared to the VLGA group (25%). Although sepsis was not part of our predefined composite outcome, its clinical relevance in the context of neonatal morbidity is undeniable. PROM is a well-known risk factor for intrauterine infection, which can contribute to both sepsis and adverse neonatal outcomes (16). While our primary focus remained on major short-term outcomes (BPD, severe IVH, severe ROP, and severe NEC), we acknowledge the nature of neonatal morbidities and the potential role of infection.

The incidence proportions of BPD (1.1%), severe IVH (15%), severe ROP (5.5%), and severe NEC (1.1%) were generally lower than those reported in major centers in developed countries. For instance, BPD rates in extremely preterm infants often ranges between 11% and 15%, and severe NEC is reported at approximately 4% in similar populations (15,17). The lower incidence proportion in our cohort may reflect differences in case mix, clinical practices, or healthcare infrastructure, as well as the relatively small sample size and brief period of observation(one year) in our study. However, the high incidence proportion of severe IVH in extremely preterm infants (33%) is known to be a risk associated with this gestational age group and highlights the importance of optimizing delivery room management and early stabilization (12,15).

In this study, gestational age was shown as the strongest predictor of adverse outcomes, consistent with prior research demonstrating that lower gestational age is associated with increased mortality and morbidity (2,5,18). Prolonged rupture of membranes (PROM) also significantly increased the risk of complications, aligning with evidence linking PROM to heightened infection risks and poor neonatal outcomes (18). Furthermore, variables such as mode of delivery, multiple births and antenatal corticosteroid use in our study did not show significant effects in multivariable models, compared to other studies where multiple births and antenatal steroids were shown as strongly associated predictors for death or adverse short-term outcomes (2,18).

Our findings reinforce the need for a multifaceted approach to neonatal care. Strategies such as timely administration of antenatal corticosteroids, prevention of PROM-related complications, and enhanced delivery room management are crucial for improving outcomes (12,15,18).

Limitations

Our study had some limitations. The study was conducted at a single institution and included only 91 neonates, limiting the generalizability of the findings to broader populations or other healthcare settings. We excluded infants transferred to our NICU due to potential differences in delivery room practices betweendifferent healthcare centers. Conducting a multicenter study that includes other hospitals in the country would provide a more comprehensive understanding of the initial management of preterm infants and help identify areas where better resource allocation and staff education could improve outcomes. Increasing the sample size and observation time in future studies could allow for a more detailed comparison of outcomes between different gestational ages in extremely preterm infants. This would provide a clearer understanding of mortality and morbidity rates for each gestational age subgroup, identifying critical periods where targeted interventions may have the greatest impact. Due to retrospective and observationaldesign of the study, potential source of bias is quality of data extracted from electronic records.

CONCLUSION

This study highlights the significant impact of gestational age and prolonged ruptures of membranes on mortality and short-term morbidities among very preterm and extremely preterm infants in a NICU setting in the largest tertiary healthcare center in Bosnia and Herzegovina. Despite comparable composite outcome rates to high-income countries, higher mortality was observed particularly in the extremely preterm infants. Future research with larger cohorts and long-term follow-up, along with more detailed data on maternal exposures and risk factors are essential in improving understanding of risk factors associated with adverse outcomes and death in premature infants in upper-middle income countries.

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Assessment of Pain Relief in Patients Undergoing Surgery for Extraforaminal Lumbar Disc Herniations at the 3-month Postoperative Follow-up.

Procjena ublažavanja boli u bolesnika podvrgnutih operaciji ekstraforaminalne hernijacije lumbalnog diska u tromjesečnom postoperativnom praćenju

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ABSTRACT

Introduction: far lateral disc herniations (FLDHs) account for up to 10% of lumbar disc herniations. Disc displacement lateral to the intervertebral foramen, primarily at the L3-L4 and L4-L5 levels, results in FLDHs. At the L5–S1 level, far-lateral disc herniations are relatively uncommon and account for 2%-4% of all lumbar disc herniations. Aim: the aim of our study was to present the pain relief during 3 months of follow up for our patients with extraforaminal lumbar disc herniation. Materials and methods: a retrospective study was conducted at the Department of Neurosurgery, Clinical Center University of Sarajevo, in the period 2019 to 2024. Patients were examined clinically and radiologically. Gender, age, symptoms prior to and following surgery, lesion side and level, and VAS scale before, after, and three months postoperatively were among the clinical data collected and included in the study. Results: the study included 34 patients, comprising 18 females (52,95%) and 16 males (47,05%), with ages ranging from 39 to 79 and a mean age of 57.35 years. FLDH were primarily found at the right L4-L5 level in 10 patients (29.4%), with predominantly on the right side (56.8%). Preoperative mean VAS scores indicated severe pain 9.06, which improved to 6.15 at discharge and further decreased to 0.51 three months post-surgery, with 82.4% of patients reporting a score of zero at that time. Conclusion: an uncommon, but clinically important condition, far lateral disc herniation has a poor prognosis and a low success rate with conservative therapy. Extraforaminal microdiscectomy provides symptom pain relief reduction with a low risk of peripro-cedural complications.

Keywords: far lateral disc herniation, magnetic resonance imaging diagnosis, clinical presentation, outcomes, surgical approach

SAŽETAK

Uvod: far lateral disc herniations (FLDH) ili ekstraforaminalna hernija diskusa čine do 10% lumbarnih hernija diska. Prolaps diska lateralno od intervertebralnog foramena, prvenstveno na nivoima L3-L4 i L4-L5, rezultira sa FLDH. Na nivou L5–S1, FLDH surelativno rijetke i čine 2%-4% svih lumbarnih hernija diska. Cilj: predstaviti ublažavanje bolit okom 3 mjeseca praćenja naših pacijenata sa ekstraforaminalnom lumbalnom hernijom diska. Materijali i metode: provedena je retrospektivna studijana Klinici za neurohirurgiju Kliničkog centra Univerziteta u Sarajevu, u periodu od 2019. do 2024. godine. Pacijenti su ispitivani klinički i radiološki. Pol, starost, simptomi prije i nakon operacije, strana i nivo lezije, kao i VAS skala prije, poslije i tri mjeseca nakon operacije, bili su među kliničkim podacima prikupljenim i uključenim u studiju. Rezultati: studija je obuhvatila 34 pacijenta, među kojima je 18 žena (52,95%) i 16 muškaraca (47,05%), sa starošću u rasponu od 39 do 79 godina i prosječnom starošću od 57,35 godina. FLDH su prvenstveno pronađene na desnom L4-L5 nivou kod 10 pacijenata (29,4%), sa dominantnom stranom na desnoj strani (56,8%). Preoperativni prosječni VAS rezultati ukazivali su na jaku bol (9,06), koja se poboljšala na 6,15 pri otpustu i dodatno smanjila na 0,51 tri mjeseca nakon operacije, uz 82,4% pacijenata koji su u to vrijeme prijavili rezultat nula. Zaključak: FLDH je neobično, ali klinički značajno stanje, sa lošom prognozom i niskom stopom uspjeha konzervativne terapije. Ekstraforaminalna mikrodiscektomija pruža smanjenje simptoma bolnosti, uz nizak rizik od perioperativnih komplikacija.

Ključne riječi: FLDH, ekstraformainalna diskus hernija, magnetska rezonanca, klinička prezentacija, ishodi, hirurški pristupkratkoročni ishodi, morbiditet

INTRODUCTION

Although Dandy was the first to report a lumbar disc herniation in the literature in the 1920s, and it required surgical care at the time, it wasn't until a few decades later that the term "far lateral disc herniation" (FLDH) first appeared in the literature. The inability of radiological methods, such as X-ray and CT myelography, to identify these lesions was probably the cause of the delay(1). In a cadaveric examination conducted in 1944, Lindblom et al. initially reported intervertebral lumbar disc prolapse externally to the spinal canal. In 1971, MacNab et al. published a report on two ineffective cases of L4-5-disc herniation that were actually L5-S1 extraforaminal disc herniation, following L5 nerve compression findings. The clinical syndrome known as FLDHs was established using a bibliography, and in 1974. Abdullah et al. characterized it as a herniation beneath and lateral to the facet, together with the nerve root compression at the exact same level (2).

Throughout the lifespan of an individual, lumbar disc herniation (LDH) continues to be one of the primary causes of 80% of low back pain. Depending on the position of the herniation, there are many forms of LDH that may be categorized, such as central, paracentral, and far-lateral herniation (3). FLDHsaccount for up to 10% of lumbar disc herniations. Disc displacement lateral to the intervertebral foramen, primarily at the L3-L4 and L4-L5 levels, results in FLDHs (4). At the L5–S1 level, far-lateral disc herniations are relatively uncommon and account for 2%–4% of all lumbar disc herniations. There have been numerous debates over the condition's clinical characteristics (5). The majority of FLDH patients arrive at the hospital with unilateral, excruciating radicular pain. The straight leg stretching test and the femoral stretch test are frequently positive. Other apparent manifestations and indicators include atrophy, loss of response, hypoesthesia caused by the compressed afflicted root and ganglion, and an overall reduction in muscular tone and strength. It was shown that individuals with long-lasting symptoms had a higher incidence of developing neuropathic pain (3). Whenever comes to detecting FLDH, magnetic resonance imaging (MRI) is the most sensitive imaging technique and a disc material obstructing the neural foramen may be seen on sagittal and parasagittal plane MRIs, while the neuronal foramina must be present in the parasagittal views. Nevertheless, the lack of fat may suggest a herniated disc, so therefore a contrast-enhanced MRI can help differentiate FLDH (non-enhancing) from malignancy(1).

It is crucial to measure and manage pain in order to implement therapies for a variety of conditions, including FLDH. Nevertheless, since pain is a subjective sensation, it is challenging to measure it accurately. The visual analog scale (VAS), a graphical approach that requires the participant to self-evaluate their pain in a 10 cm-length horizontal line with various pain legends, is the basis for the widely accepted method of measuring pain in adults. Scores range from 0 (there is no pain) to 10 (the worst possible pain) (6). Hayes and Patterson introduced the visual analog scale (VAS) as a method of assessing pain in 1921. The data can be used to compare pain amongst patients with comparable diseases or to monitor a patient's pain as it progresses (7).

Understanding the far lateral region's anatomy is crucial for both diagnostic and surgical care. Anatomically, the extraforaminal area is found laterally, between the upper and lower pedicles, while its borders are the facet joint dorsally, the upper portion of the superior facet medially, and the intervertebral disc and vertebral body anteriorly (2). Because of this position surgeons frequently hesitate to do surgery on FLDHs and instead choose to manage the condition conservatively. When patients exhibit clinical signs that are uncontrollable with conservative measures or techniques like transforaminal epidural injections, surgical alternatives are taken into consideration.

For the treatment of far lateral disc herniations, five fundamental surgical techniques are available: medial facetectomy, total facetectomy, intertransverse approach, and extreme lateral and trans pars opening. Surgeon expertise determines the surgical procedure that will be used (8).

AIM

The aim of our study was to present the pain relief during 3 months of follow up for our patients with extraforaminal lumbar disc herniation.

MATERIALS AND METHODS

A retrospective study was conducted at the Department of Neurosurgery, Clinical Center University of Sarajevo (CCUS), in the period from January 2019 to December 2024. Clinical characteristics of the patients were investigated, as well as radiological components such as magnetic resonance imaging (MRI) of the lumbar spine along with symptoms at the time of admission. For the purpose of the study, radiological imaging data were obtained from the hospital's IMPAX® Agfa ™ system, while medical record data were gathered from the E medIT® hospital information system. We included all patients with radiological confirmed FLDH at lumbar spine (Figure 1).

The research excluded patients who had undergone prior spinal surgery for lumbar disc herniation or any other cause. Furthermore, the study did not include individuals whose preoperative examinations revealed spinal instability, infection, or tumor. Moreover, the research excluded individuals with pediatric age (<18 years old), previous surgery, spinal nerve tumors, and ones that have been treated conservatively.

All patients were treated with posterior approach for far lateral disc herniation involving positioning the patient in a genopectoral or prone position and making a paramedian incision to access the spinal elements. Following soft tissue dissection, a partial fasetectomy is performed to expose the affected nerve root, along with a foraminotomy to aid in decompressing the nerve. The herniated disc material is then carefully removed using microdiscectomy techniques to preserve surrounding structures.

The post-operative assessment included complications, a VAS scale upon discharge, and a three-month follow-up period.

Statistical analysis

Descriptive statistics were employed to analyze the data. Categorical data are shown as frequency and percentage ratios, while quantitative data are represented as mean values with standard deviations. The two-sample t-was used to analyze continuous variables. The data analysis was performed using the Microsoft Excel software. A p-value of <0.05 was considered statistically significant.

RESULTS

The study consisted of a total of 34 patients-18 females (52.95%) and 16 males (47.05%), whose ages ranged from 39 to 79 years, with a mean age of 57,35+-10,27 years, there was no difference between male and female (p=0.162).

There were lesions at the left L4-L5 level in eight patients (23.52%), the right L4-L5 level in ten patients (29.41%), the left L3-L4 level in four patients (11.76%), the right L3-L4 level in two patients (5.88%), the left L5/S1 level in two patients (5.88%) and right L5/S1 level in seven patients (20.58%)and one left L2/L3 (2.94%).Disc herniation including intraforaminal and extraformainal location occurred in 11 patients (32.4%). Far lateral disc herniation occurred in 19 patients on the right side (56.8%).All patients had the same side clinical symptoms as FLDH side.

The mean VAS score preoperative was 9.06+-0.68, where all patients hadVAS 8 or above, indicating a severe pain.At discharge the meanVAS score was 6.15+-0.73, indicating good pain relief(p <0,001) and at 3 months after surgery the medain VAS score was 0 (IQR 0-0)(p <0,001), where most patient had been VAS score 0, 82.4%, one patient did not have improvement on VAS score after 3 months of follow up.There was no difference between preoperative VAS score between male and female patients (p = 0.172). The mean preoperative VAS score was higher at levels L4/L5 and L5/S1 when compared to L2/L3 and L3/L4 (mean 9.33 and mean 8; p < 0.00001). The mean value of VAS at admission for right sided FLDH (19 patients) was 9.24 and for left sided (15 patients) 8.8, with significant difference (p=0.026).VAS score difference during 3 months follow up was presented in the Figure 2. Extraforaminal disc herniaton had 23 patients with mean VAS admission score 8.9, and 11 patients had intraforaminal and extraforaminal disc herniation with mean VAS admission score 9,36, with significant difference (p=0.038).

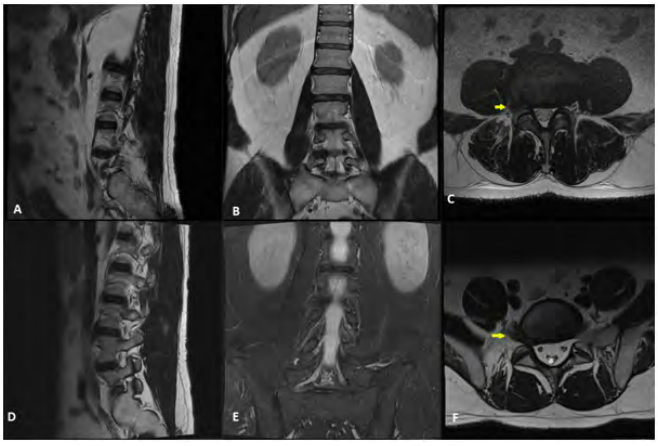

Figure 1.**MRI of lumbar spine of a patient with far lateral disc herniation, only extraforaminal component (A-C). MRI of lumbar spine of a patient with far lateral disc herniation, extraforaminal and intraforaminal component (D-F).Yellow arrows pointing on the disc herniation**.

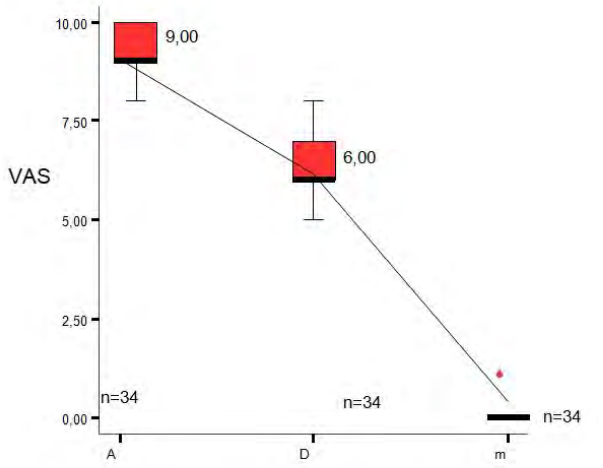

Figure 2 **VAS dinamics during 3 months follow up. VAS - visual analouge scale; A-VAS ata dmission; D-VAS at dishcharge; m-VAS after 3 months.**

DISCUSSION

In this study, we demonstrated that FLDH is a significant cause of severe pain. All patients who underwent microsurgical intervention for FLDH experienced marked pain relief immediately following surgery, which was improved during the follow-up period.

Roughly 7-10% of lumbar disc herniations are caused by far lateral lumbar disc fragments (9).This is a unique type of lumbar disc herniation andmore specialized expertise is needed for clinical presentation, diagnosis, and therapy, which are more demanding than usual.According to a 2009 study by O'Toole et al., extraforaminal disc herniations are more common in relatively older people than paramedian LDHs, with a peak in the sixth decade of life (10).Comparably, the patients in our study had ages ranging from 39 to 79 years, with a mean of 57.35 years.There is little difference in the distribution of gender between the two groups. By definition, a far lateral disc herniation is a disc herniation or fragment that lies beneath and lateral to the vertebral facet, which is hidden on typical imaging of the spinal canal. However, far lateral disc herniations are frequently overlooked in diagnosis. One possible explanation is a lack of effective diagnostic methods, as well as a lack of adequate neurologic examination and insight into the dermatomal distribution of pain. Undoubtedly, further research is necessary.

FLDH are also referred to as foraminal, intraforaminal, far lateral, or extreme lateral disc herniation (1). A detailed preoperative diagnosis and identification of an extracanalicular herniated disc are prerequisites for selecting the best surgical approach. Myelographic images are unable to adequately represent root compression because it occurs beyond the lateral expansion of the subarachnoid space. Although FLDHs were difficult to detect before the invention of computed tomography (CT), disc herniations in intra- and extraforaminal regions may now be detected in great detail using CT and MRI. This suggests that MRI is the gold standard for identifying spinal degenerative diseases if the right protocol is followed.In our study, we performed an MRI of the LS spine on all patients, which clearly revealed a lateral disc herniation. However, despite improvements in neuroimaging, FLDH diagnosis could still be challenging.

In fact, slice thickness and field lateral extension typically pose limitations to regular spine imaging. In addition, concomitant degenerative changes such as stenosis or intracanalicular disc bulging may obstruct visualization of radicular compression within or laterally to the foramen (11).

There is also a tendency to focus neurosurgical work on the intracanalicular component of the disc, while giving less attention to the extraforaminal component. In every scenario, when the patient's clinical picture changes and there are no abnormalities inside the spinal canal, the foramen must be examined. Indirect symptoms of compression include nerve ganglion edema and the resolution of complaints following corticosteroid therapy. The femoral stretch test is usually positive in these patients, lateral bending to the side of the disc herniation can replicate discomfort and paresthesia, and pain is frequently more intense than in central disc herniations - possibly as a result of direct compression of the dorsal root ganglion.

The most common levels in the research done beforeFuentes et al.'s study were L4–L5, followed by L3–L4, L5–S1, L2–L3, and L1–L2, whilelevels L3–L4 were the most common in their research (12). However, the L4–L5 has the highest absolute frequency occurrence in our analysis.

Short-term follow-up six months following surgery revealed outstanding success based on pain alleviation evaluated by VAS classification in the clinical outcomes of the study by Eicker et al. in 2013. A patient satisfaction survey assessed certain persistent symptoms as not severe. Relief of leg pain in particular was considered a significant advantage; this may be related to the extreme discomfort resulting from compression of the spinal ganglion as well as the exiting nerve root (13). Similarly, the meanVAS score for radicular leg pain significantly improved in our study between the preoperative, postoperative, and final follow-up evaluations, which occurred three months later. These results demonstrated noteworthy levels of symptomatic and functional advancement for the 34 patients.

According to the intrinsically challenging anatomical access to the lateral interpedicular compartment without the probability of damaging nerves or the overlying facet joint, which could potentially put the patient at risk of an unstable spine requiring spinal fusion surgery in the future, the surgical treatment of FLDHs has remained an exhausting procedure for many spine surgeons. Due to this fact, surgeons frequently hesitate to do surgery on FLDHs and instead choose to manage the condition conservatively (1). Nonoperative management success rates vary from 10% to 71%. FLDHs have been treated surgically using a variety of procedures for individuals who do not respond to anticipated treatments (10). Nevertheless, the accompanying radiological images of the partial lateral fasetectomy in our investigation did not demonstrate any spinal instability.

This study is subject to several limitations, primarily due to its retrospective design and the relatively small sample size of 34 patients.The retrospective nature of the study may introduce biases related to data collection, such as incomplete records or reliance on subjective patient reports, which can affect the reliability of the findings.

CONCLUSION

In conclusion, far lateral disc herniation is a rare but significant condition with a poor prognosis and low success rates for conservative treatment. Microsurgical treatment for this condition results in significant pain relief during the period of 3 months, with low rate of complications.

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Assessing the Role of Demographic and Tumor Characteristics in Histological Regression of Primary Cutaneous Melanoma

Evaluacija uloge demografskih i tumorskih karakteristika u histološkoj regresiji primarnog kožnog melanoma

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ABSTRACT

Introduction: melanoma is a highly aggressive skin cancer, and its incidence has been increasing globally. Histological regression in primary cutaneous melanoma is an immunological process that can lead to the partial or complete disappearance of the tumor. It may be associated with favorable prognostic outcomes, but its role in patient prognosis remains debated. Aim: to investigate the clinicopathological features associated with histological regression in primary cutaneous melanoma and assess its prognostic significance. Materials and methods: this retrospective study analyzed 105 Bosnian patients diagnosed with primary cutaneous melanoma between 2021 and 2025. Data collected included demographic factors (age, sex, melanoma location), pathological features (Breslow thickness, ulceration, and regression), and the extent of tumor spread (localized, regional, or distant metastasis). Statistical analysis was performed to identify significant associations between histological regression and clinicopathological characteristics. Results: histological regression was observed in 51 (48.6%) of the 105 patients. The median age was 62 years, with 57.1% of cases in males. Melanomas with regression were thinner (Breslow thickness ≤1 mm) compared to those without regression ($p < 0.0001$). Ulceration was less frequent in melanomas with regression ($p = 0.007$). Patients with stage I and II melanomas had a higher likelihood of regression ($p = 0.036$). Multivariate logistic regression identified Breslow thickness as a strong predictor of regression (OR = 0.09, $p < 0.0001$). Conclusion: our study demonstrates that thinner melanomas (Breslow thickness ≤1 mm) are significantly more likely to exhibit histological regression. Regression was more common in patients with localized melanoma (stages I and II), suggesting its potential role as a favorable prognostic factor. These findings underline the importance of Breslow thickness as a key determinant in the presence of regression and highlight the need for further research to better understand its impact on melanoma prognosis.

Keywords: melanoma, histological regression, breslow thickness, ulceration, immunological response, skin cancer

SAŽETAK

Uvod: melanom je visoko agresivan karcinom kože, čija učestalost raste širom svijeta. Histološka regresija u primarnom kožnom melanomu je imunološki proces koji može dovesti do djelomičnog ili potpunog nestanka tumora. Ovaj proces može biti povezan sa povoljnim prognostičkim ishodima, ali njegova uloga u prognozi pacijenata i dalje je predmet rasprave. Cilj: istražiti kliničko-patološke karakteristike povezane s histološkom regresijom u primarnom kožnom melanomu i procijeniti njegovu prognostičku značajnost. Materijali i metode: ova retrospektivna studija analizirala je 105 pacijenata iz Bosne i Hercegovine, dijagnostikovanih s primarnim kožnim melanomom u periodu od 2021. do 2025. godine. Prikupljeni podaci uključivali su demografske faktore (dob, spol, lokacija melanoma), patološke karakteristike (Breslow debljina, ulceracija i regresija) i opseg širenja tumora (lokalizirani, regionalni ili udaljeni metastaze). Statistička analiza je provedena kako bi se identificirale značajne povezanosti između histološke regresije i kliničko-patoloških karakteristika. Rezultati: histološka regresija zabilježena je u 51 (48,6%) od 105 pacijenata. Srednja dob pacijenata bila je 62 godine, a 57,1% slučajeva bilo je kod muškaraca. Melanomi sa regresijom bili su tanji (Breslow debljina ≤1 mm) u odnosu na one bez regresije ($p<0,0001$). Ulceracija je bila rjeđa u melanomima sa regresijom ($p=0,007$). Pacijenti sa stadijem I i II melanomom imali su veću vjerojatnost za regresiju ($p=0,036$). Multivarijantna logistička regresija identificirala je Breslow debljinu kao snažan prediktor regresije (OR = 0,09, $p < 0,0001$). Zaključak: naša studija pokazuje da su tanji melanomi (Breslow debljina ≤1 mm) značajno češće skloni histološkoj regresiji. Regresija je bila češća kod pacijenata sa lokaliziranim melanomima (stadiji I i II), što sugerira da bi mogla imati potencijalnu ulogu kao povoljan prognostički faktor. Ovi nalazi podvlače značaj Breslow debljine kao ključnog faktora prisustva regresije i naglašavaju potrebu za daljim istraživanjima kako bi se bolje razumio njen uticaj na prognozu melanoma.

Ključne riječi: melanom, histološka regresija, breslow debljina, ulceracija, imunološki odgovor, karcinom kože

INTRODUCTION

Melanoma is a highly aggressive skin cancer that arises from melanocytes, and its incidence has been increasing globally in recent years. Early detection and appropriate treatment are crucial for improving survival outcomes in melanoma patients.

Regression in primary cutaneous melanoma is an immunological process that leads to the partial or complete disappearance of the tumor (1). It can be identified both clinically (macroscopically) and histologically (microscopically) (2). Histologic regression of primary melanoma is generally defined by most authors as the partial, segmental, or complete replacement of melanoma cells with a varied host response. This response can include a range of elements such as a mono-nuclear infiltrate of varying density, melanophages, dermal fibrosis, and increased vascularity in the dermis, often accompanied by varying degrees of epidermal thinning. It is important to note that histologic regression is frequently observed even in the absence of clinically evident regression (3). Clinical signs of regression include areas of depigmentation within or around the melanoma. The color may be white, red, blue, or gray. Melanoma regression tends to occur in adult or elderly patients and is extremely rare in young people (4). Histological regression has been described in 10-35% of the primary melanoma tumors (5).

Determining which patients are more likely to develop melano mas with histological regression could help identify a subgroup with distinct prognostic outcomes. Histological regression may act as a significant prognostic marker, as multiple melanoma cases have been documented in which regional metastases (such as cutaneous or lymph node involvement) emerged despite the complete regression of the primary melanoma or an unknown primary tumor, suggesting a possible relationship between regression and the development of metastasis. However, more recent studies suggest that histologic regression in primary melanoma may be linked to a negative sentinel lymph node (SLN) status (3). It was shown that there was a lower likelihood of death in patients with melanomas with histological regression compared to those without (6).

As a result, the prognostic significance of regression in melano ma patients continues to be a topic of debate.

AIM

The aim of the study was to investigate the independent effect of clinicopathological features associated with the presence of histological regression in cutaneous invasive melanomas.

MATERIALS AND METHODS

This retrospective study analyzed Bosnian patients diagnosed with primary cutaneous melanoma who presented to the Reconstructive and Plastic Surgery Clinic at the Clinical Center, University of Sarajevo, between 2021 and 2025. Eligible cases included patients aged over 18 years with a confirmed diagnosis of primary cutaneous melanoma, supported by an appropriate histopathological report. Melanomas in situ were excluded from the analysis.

Data collected for each patient included demographic information such as age at diagnosis, sex, and melanoma location. Pathological data included Breslow thickness (in mm), ulceration (present or absent), and regression (present or absent). The extent of tumor spread at the time of initial presentation was classified into three categories: localized disease (no evidence of satellite or in-transit, nodal, or distant metastases), regional disease (including satellite/in-transit metastasis, regional nodal micrometastasis, or regional nodal macrometastasis), and distant metastasis.

RESULTS

A total of 105 eligible cases were included in the study. Among these, 51 cases (48.6%) exhibited histological regression. The median age of the patients was 62 years (IQR: 52.5, 73.5). Of the total cases, 57.1% were male, and 42.9% were female. At the time of diagnosis, 89 cases (84.8%) were diagnosed with stage I and II melanoma, while the remaining 16 cases (15.2%) presented with locoregional or distant metastasis.

Regarding Breslow thickness, 40.0% of melanomas had a thickness ≤ 1 mm, 20.0% were between 1.1 and 2.0 mm, 19.0% were between 2.1 and 4.0 mm, and 21.0% had a Breslow thickness greater than 4.0 mm.

Melanomas with regression had Breslow thickness ≤ 1 mm in 64.7% of cases, thickness 1.1–2.0 mm in 19.6% of cases, and they were thicker than 2.0 mm in 15.7% of cases. Melanomas without regression had Breslow thickness ≤ 1 mm in 16.7% of cases, and were more frequently thicker than 2.0 mm (63.0%) compared to melanomas with regression. (Figure 1)

There was no significant association between sex and the presence of regression, as indicated by an odds ratio (OR) of 1.14 (95% CI: 0.52–2.51) and a p-value of 0.735, suggesting that gender does not influence the likelihood of regression in this study population. The median age at diagnosis was 62 years (IQR: 53–76) for patients without regression and 62 years (IQR: 52–70) for those with regression, with a p-value of 0.278, indicating no significant difference in age between the two groups.

A significant difference in Breslow thickness was observed between patients with and without regression. The median Breslow thickness was 2.7 mm in patients without regression, while it was significantly thinner in those with regression, with a median of 0.6 mm ($p < 0.0001$). Melanomas with a Breslow thickness ≤ 1.0 mm were significantly more likely to show regression, with 64.7% of cases in the regression group compared to only 16.7% in the non-regression group ($p < 0.0001$). The odds of regression were lower in melanomas with a Breslow thickness > 1.0 mm (OR: 0.48, 95% CI: 0.35–0.65).

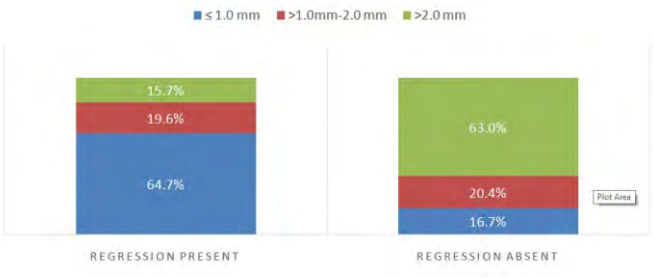

Figure 1 **Breslow thickness categories in melanomas with regression and melanomas without regression.**

Melanomas with regression were most commonly observed on the trunk, accounting for 54.9% of cases with regression. The head/neck region followed, with 15.7% of cases showing regression, while the upper and lower extremities accounted for 29.4% of cases with regression. Melanomas without regression were most commonly found on the trunk, representing 46.3% of cases without regression. The upper and lower extremities accounted for 31.5%, while the head/neck region had 22.2% of cases without regression. No significant association was found between the primary site and the presence or absence of regression in melanomas (p = 0.60).

A significant association was found between ulceration and the presence of regression. Ulceration was present in 38.9% of melanomas without regression, but only 15.7% in melanomas with regression (p = 0.007). The odds of regression were lower in ulcerated melanomas (OR: 0.29, 95% CI: 0.12–0.74).

Patients with melanoma confined to the primary site (stage I and II) were significantly more likely to have regression, with 92.2% of patients in the regression group diagnosed at this stage, compared to 77.8% in the non-regression group (p = 0.036). The odds of regression were lower in patients with locoregional or distant metastasis (stage III or IV) (OR: 0.29, 95% CI: 0.09–0.99) (Table 1)

We performed a multivariate logistic regression analysis to investigate the independent association of age, sex, Breslow thickness category, melanoma localization, and ulceration with histological regression. For all cases (n = 105), multivariate logistic regression analysis revealed that Breslow thickness was significantly associated with the presence of histological regression. Melanomas with a Breslow thickness > 1.0 mm were much less likely to show regression compared to those with a Breslow thickness ≤ 1.0 mm (OR = 0.09, 95% CI: 0.04–0.29, p < 0.0001). No significant associations were found between histological regression and age (OR = 1.56, 95% CI: 0.51–4.74, p = 0.435), sex (OR = 1.00, 95% CI: 0.38–2.59, p = 0.996), or primary site (head/neck, trunk, or upper/lower extremities).

These results suggest that Breslow thickness is a strong predic tor of regression in invasive melanomas, while other clinicopathological factors such as age, sex, and primary site do not significantly influence the occurrence of regression.0.65).

Table 1 **Clinicopathological features of patients with invasive melanoma according to histological regression (n = 105).**

Variables	In patients with regression absent (n=54)[a]	In patients with regression present (n=51)[a]	Frequency of regression	OR (95% CI) of regression present[b]	p-value[b]
Sex, n(%)					
Female	24 (44.4)	21 (41.2)	46.7%	Ref	0.735
Male	30 (55.6)	30 (58.8)	50.0%	1.14 (0.52-2.48)	
Age at diagnosis, median (IQR), y	62 (53. 76)	62 (52.70)			0.278
Age, years, n (%)					
≤50	13 (24.1)	12 (23.5)	48.0%	Ref	
> 50	41 (75.9)	39 (76.5)	48.8%	1.03 (0.42-2.53)	0.947
Breslow thickness median (IQR), mm	2.7 (1.4 - 5.6)	0.6 (0.4. - 1.7)			**<0.0001**
Breslow thickness categories, n(%)					
≤1.0 mm	9 (16.7)	33 (64.7)	78.6%	Ref	
> 1.0 mm	45 (83.3)	18 (35.3)	28.6%	**0.48 (0.35-0.65)**	**<0.0001**
Ulceration, n (%)					
Absent	33 (61.1)	43 (84.3)	56.6%	Ref	
Present	21 (38.9)	8 (15.7)	27.6%	**0.29 (0.12-0.74)**	**0.007**
Primary site, n (%)					
Head/neck	12 (22.2)	8 (15.7)	40.0%	Ref	
Trunk	25 (46.3)	28 (54.9)	52.8%	0.59 (0.21-1.69)	0.602
Upper/lower extremity	17 (31.5)	15 (29.4)	46.9%	0.78 (0.33-1.89)	0.451
Tumor spread, n (%)					
Primary only (stage I, II)	42 (77.8)	47 (92.2)	52.8%	Ref	
Locoregionaland distant metastasis (stage III, IV)	12 (22.2)	4 (7.8)	25.0%	**0.29 (0.09-0.99)**	**0.036**

[a] Percentages are presented by column. [b] Odds ratios and p-values from univariate logistic regression. Mann-Whitney test for thecomparison of medians. Statistically significant values are shown in bold character.

Table 2 **Multivariate logistic regression analysis of the association of the presence ofhistological regression with clinicopathological characteristics in invasive melanomas in all cases and in subgroup analysis of stage I and II melanomas.**

Variable	All cases (n=105)		Stage I and II melanomas (n=	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age years				
≤ 50	Ref	0.435	Ref	0.334
> 50	1.56 (0.514.74)		1.77 (0.565.61)	
Sex				
Female	Ref	0.996	Ref	0.587
Male	1.00 (0.382.59)		1.34 (0.463.91)	
Breslow thickness, mm				
≤ 1.0	Ref	**0.0001**	Ref	**0.0001**
> 1.0	**0.09 (0.040.29)**		**0.09 (0.030.26)**	
Primary site				
Head/neck	Ref		Ref	
Trunk	1.74 (0.515.95)	0.773	1.42 (0.385.28)	0.601
Upper/lower extremity	1.22 (0.324.63)	0.371	1,77 (0.427.39)	0.436

Multivariate analysis adjusted for all variables shown in Table.
OR: odds ratio, CI: confidence interval.
Statistically significant values are shown in bold characters

Furthermoret, we explored the association of clinicopatho logical features with regression in the subgroup of stage I and II melanomas. In univariate logistic regression analysis, Breslow thickness was significantly associated with the presence of histological regression in stage I and II melanomas, with melanomas ≤1.0 mm being more likely to show regression (OR=0.12, 95% CI: 0.04-0.37).

We then performed a multivariate analysis in stage I and II melanomas to investigate the independent association of age, sex, Breslow thickness, melanoma localization, and subtype with histological regression. Patients with Breslow thickness >1.0 mm were significantly less likely to have histological regression (OR=0.09, 95% CI:0.03-0.26, p=0.0001) (Table 2).

In stage III and IV melanomas (n=16), across both univariate and multivariate analyses, noclinicopathological variables (age, sex, Breslow thickness, primary site) showed a statistically significant association with the presence of histological regression.

DISCUSSION

In our study, we examined the clinicopathological features associated with histological regression in primary cutaneous melanomas. Our findings highlight several factors that may influence the occurrence of histological regression.

We observed that thinner melanomas (≤1.0 mm) exhibited a higher frequency of regression (64.7%) compared to thicker melanomas (>1.0 mm), which had a regression frequency of 35.3%. This observation aligns with previous research. For example, a study byVincenzo et al. assessing 713 patientswith primary cutaneous melanomas found that the presence of regression was significantly associated with a lower Breslow thicknessindicating that regression is more common in thinner lesions (7).

Our study also found a significant association between the absence of ulceration and the presence of regression. Melanomas without ulceration had a lower odds ratio for regression (OR: 0.29), suggesting that ulceration might be linked to a more aggressive tumor phenotype that is less susceptible to immune-mediated regression.This finding is consistent with the notion that ulceration is an indicator of tumor aggressiveness (8).

In our cohort, sex and age did not show significant associations with histological regression.This finding contrasts with some studies that have reported varying impacts of these factors on regression.Previous research has indicated that melanomas exhibiting histological regression were more commonly found in older patients and males, while less frequently associated with the nodular melanoma (NM) subtype (2,9).

On the other hand, a comprehensive analysis of 14 studies comprising over 10,000 patients found that histological regression was associated with a lower relative risk of death, but age was not identified as a significant modifying factor. This suggests that while regression may confer a survival advantage, age does not significantly modify this association (6,9).

In contrast to some studies suggesting a male predominance in histological regression, our analysis did not find a significant association between sex and regression status.This discrepancy may be attributed to differences in study populations, methodologies, or sample sizes. For example, a study involving 8,693 melanoma cases reported that moderate and severe regression were observed slightly more frequently in males. However, our cohort's characteristics might differ, potentially accounting for the observed differences (1).

Dessinioti et al in their research showed that male sex, age, and nodular subtype were independently associated ith histological regresion (10). These results suggest possible sex-related and subtype dependent differences in the immunological response in melanomas. Since histological regression has been linked to a more favorable prognosis, identifying associated factorssuch as sexcould provide insight into potential biological mechanisms underlying the improved survival rates observed in males undergoing immuno-therapy. This association may also encourage further research into sex-specific characteristics influencing melanoma outcomes. Currently, there is a lack of studies exploring how histological regression affects melanoma response to immunotherapy. Determining which patients are more likely to develop melanomas exhibiting regression could help define a subgroup with distinct immunological responses, potentially impacting both prognosis and treatment efficacy.

CONCLUSION

Our study demonstrates that thinner melanomas (Breslow thickness ≤1 mm) are significantly more likely to exhibit histological regression. Regression was more common in patients with localized melanoma (stages I and II), suggesting its potential role as a favorable prognostic factor. These findings underline the importance of Breslow thickness as a key determinant in the presence of regression and highlight the need for further research to better understand its impact on melanoma prognosis. Additionally, the lower frequency of ulceration in melanomas with regression may indicate a less aggressive disease course. Given the potential implications for patient management and treatment strategies, future studies should focus on exploring the mechanisms of regression and its possible role in improving patient outcomes. Furthermore, the association of histological regression with other molecular markers could provide insights into more personalized and targeted therapeutic approaches for melanoma patients.

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Outcomes of Low-Pressure Pneumoperitoneum on Pain and Inflammation in Laparoscopic Cholecystectomies

Ishodi pneumoperitoneuma niskog pritiska na bol i upalu kod laparoskopskih holecistektomija

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ABSTRACT

Introduction: in laparoscopic cholecystectomy, the standard pneumoperitoneum pressure is set at 12–14 mmHg. Many societies advocate working at the lowest possible pressure that allows adequate exposure of the operative field. Numerous studies to date have described the advantages of working with low-pressure pneumoperitoneum in terms of lower postoperative pain and more hemodynamically stable patients. While very few describe the effects on inflammatory factors and cytokines. Aim: to evaluate the effect of low-pressure pneumoperitoneum compared to standard-pressure pneumoperitoneum on postoperative pain and inflammatory markers. Materials and methods: a prospective, randomized, controlled clinical trial, which included patients undergoing laparoscopic cholecystectomy in an elective program. Patients were randomized to a consistent pressure level: low pressure (8–10 mmHg) versus standard pressure (12–14 mmHg) in a 1:1 ratio. We collected and analyzed preoperative variants. The study enrolled 60 patients in each group. Patients treated with low pressure had significantly lower mean pain scores at 6 hours postoperatively (p-value = 0.021) compared to the standard pressure group. So many of the inflammatory markers showed better results in the low-pressure group compared to the standard-pressure group, but the effect was shown to be statistically significant in the IL-6 value. There were no statistically significant differences between the two groups in terms of total operative time and surgical complexity and in the hands of less experienced surgeons. Conclusion: laparoscopic cholecystectomy at lower pneumoperitoneum pressures is associated with less postoperative pain and a smaller increase in inflammatory markers.

Keywords: laparoscopic cholecystectomy, low pneumoperitoneum pressure, pain, inflammatory marker

SAŽETAK

Uvod: kod primijene laparoskopske holecistektomije standardni pritisak pneumoperitoneuma je postavljen na 12-14 mmHg. Mnoga dosadašnja društva su zagovornici rada na najnižem mogućem pritisku koji omogućava da se adekvatno izloži operativno polje. Dosadašnja brojna istraživanja su opisala prednosti rada kod upotrebe niskog pritiska pneumopertineuma u smislu nižeg postoperativnog bola i hemodonamski stabilnijih pacijenata. Dok vrlo mali broj opisuje učinke na faktore upale i citokine. Cilj: procijeniti učinak pneumoperitoneuma niskog pritiska u odnosu na pneumoperitoneum standardnog pristiska na postoperativni bol i inflamatorne markere. Materijali i metode: prospektivno, randomizirano, kontrolirano kliničko ispitivanje, koje uključuje pacijente koji su podvrgnuti laparoskopskoj holecistektomiji u elektivnom programu. Pacijenti su randomizirani skladno visini pritiska: niski pritisak (8-10 mmHg) prema standardnom pritisku (12–14 mmHg) u omjeru 1:1. Skupili smo i učinili analizu preoperativnih varijabli. U istraživanje je uzeto po 60 pacijenata u svaku grupu. Pacijenti tretirani niskim pritiskom su imali znatno nižu srednju vrijednost bola 6 sati nakon operacije(p-vrijednost = 0,021) u osnosu na grupu tretiranu sa standardnim pritiskom. Toliko od toliko inflamatornih markera pokazali su bolje rezultate u grupi tretiranoj niskim pritiskom u odnosu na onu tretiranu standardnim pritiskom, ali se pokazalo da efekat je bio statistički značajan u vrijednosti IL-6. U pogledu ukupnog operativnog vremena i težine operacije nisu dobijeni statistički značajni rezultati između dvije grupe i u rukama hirurga sa manje iskustva. Zaključak: laparoskopska holecistektomija na nižim vrijednostima pritiska pneumopertineuma u vezi je sa manjim postoperativnim bolom i manjim porastom inflamatornih markera.

Ključne riječi: laparoskopska holecistektomija, niski pritisak pneumopertineuma, bol, marker inflamcije

INTRODUCTION

The first laparoscopic cholecystectomy was performed by Professor Mühe from Germany in 1985. Since then, it has become the gold standard for gallbladder removal in various indications (1). A large number of laparoscopic procedures are performed with a standard pressure pneumoperitoneum (12-15 mmHg). Low-pressure pneumoperitoneum is a challenge. Studies have compared low pressure with standard pressure in terms of postoperative pain, complications, length of hospital stay, stress response and surgeon satisfaction (2). In our randomized trial, we compared pneumoperitoneum pressures in terms of pain, inflammatory markers, operative time and surgeon satisfaction.

MATERIALS AND METHODS

Design and participants: the study sought to determine a statistical difference in markers of pain and inflammation by comparing two groups in a 1:1 ratio. The study was prospective. Enrollment was open to patients older than 12 years and those with an ASA score of 1 or 2 (American Society of Anesthesiologists) with gallbladder symptoms and scheduled for elective laparoscopic cholecystectomy. Patients with ultrasound-confirmed acute cholecystitis and those undergoing upper abdominal surgery, as well as pregnant and lactating women, were excluded from the study.

Intervention: patients were randomly categorized using a computer-generated chart and scheduled for 1 of the following 2 procedures; standard pressure pneumoperitoneum (SP group, 12–14 mmHg), low pressure pneumoperitoneum (LP group, 9–11 mmHg). A piece of paper with the name of the procedure was placed in an envelope, and each envelope was numbered according to the order of the numbers in the table. Those in the intervention group will undergo laparoscopic cholecystectomy under low-pressure pneumoperitoneum, defined as a set point of gas insufflation between 9 and 11 mmHg, and those in the control group will undergo laparoscopic cholecystectomy under standard-pressure pneumoperitoneum. The set point of insufflation is between 12 and 14 mmHg. The pressure at the beginning of the operation started at 9 mmHg for the low-pressure group and 12 mmHg for the standard-pressure group, and at the request of the surgeon, the pressure will be increased by two points each time. Trocars will be inserted at a pressure determined by each group. Pain outcomes were assessed using the 11-point Brief Pain Scale (SPS-11) as perceived by the patient at 6 h, 12 h, 24 h, and 7 days after surgery. The following inflammatory markers were examined: white blood cell count (WBC) (10^3 cells/mm), platelet count (Plt) (10^9/L), erythrocyte sedimentation rate (ESR) (millimeters per hour), C-reactive protein (CRP) level (mg/L), albumin (Alb -6) level (ILg/6kin-6) level (ILg/6kin-6) (pg/mL). They were determined by taking blood samples from the subjects for analysis. Pain scores were assessed based on the VAS (visual analog scale) (13). The test used to assess the distribution of numerical variables was the Kolmogorov-Smirnov test. BMI (body mass index) - The formula for BMI is weight in kilograms (kg) divided by height in meters squared (m2). Blood samples were taken the morning after surgery as a baseline for all markers of the inflammatory process. Twenty-four hours after surgery, the markers were reassessed.

Outcomes: the primary outcome was to search for a statistically significant difference in pain at four time points 6h, 12h, 24h and 7 days after surgery. Secondary outcomes were to search for a difference in the time of surgery and the severity of the surgery between the two groups. There were 120 subjects divided into two equal groups. Color codes were used for randomization, data entry and analysis. Allocation was random, according to a computer-generated list.

Statistical analysis: the analysis was performed using SPSS Statistics 24.0. We analyzed gender, severity of surgery, ASA score, smoking status using a Chi square table. Student t test analyzed the mean value of hospitalization, total time of surgery, gas insufflation time. Mann-Whitney U test analyzed the mean pain intensity. The following inflammatory markers (WBC, Plt, ESR, CRP, albumin, IL-6) were analyzed using the Welch t test. P value was set at 0.05 for statistical significance.

RESULTS

A total of 120 patients were included in the analysis, 60 patients in each study group (n = 60). The sample had a normal distribution. Age and BMI were analyzed using the Student t test (Table 1). Gender, smoking status and ASA score were analyzed using the Chi-square cross-tabulation (Table 2). The mean duration of insufflation time, days of hospitalization, and total operative time were similar in both groups without statistically significant differences. The analysis was performed using the Student's t-test (Table 3). There was no significant difference in the severity of the surgery between the two groups using the Chi-square cross-tabulation (Table 4). There was no statistically significant correlation between operator level and surgical difficulty (p-value = 0.369) using correlation, Spearman's correlation (-0.091) for all cases, Spearman's correlation (-0.221) for the low pressure group, Spearman's correlation (-0.039) for the standard pressure group. In the low pressure group using Mann-Whitney U test, it was observed that the average pain intensity was lower and a statistically significant difference was observed postoperatively 6h after surgery in the low pressure group. (Table 5), (Fig. 1). The total number of analgesics was observed in the two groups and there was no statistically significant difference (p-value = 0.412), but the mean number of analgesias was lower in the low pressure group. Inflammatory markers were assessed before and after surgery using the Welch t test and p value (Table 6).

Table 1 **Analysis of BMI and age between the two groups.**

	Standard pressure group Mean±SD	Low pressure group Mean±SD	p-value
Age (year)	40.76±12.45	42.76±14.45	0.67
BMI (kg/m2)	27.75±4.32	28.21±4.32	0.58

There is no significant difference in mean between both groups in terms of BMI and age

Table 2 **Analysis of gender, smoking and ASA score between the two groups**.

		Standard pressure group n (%)	Low pressure group n (%)	p-value
Gender	Male	9 (15%)	11 (18,3%)	0.500
	Female	49 (81,7%)	51(85%)	
Smoking status	Smoker	18 (30%)	18 (30%)	0.562
	Nonsmoker	42 (70%)	42 (70%)	
ASA score	I	33 (55%)	25 (41,7%)	0.531
	II	37 (61,7%)	25 (41,7%)	

There is no significant difference in mean between both groups in terms of gender, smoking status and ASA score.

Table 3 **Analysis of duration of the operation, gas insufflation time, days after surgery between the two groups**.

	Standard pressure group Mean±SD	Low pressure group Mean±SD	p-value
Duration of the operation (min)	53.1±18.63	54.8±16.42	0.793
Gas insufflation time (min)	42±17.9	43±16.71	0.812
Days after surgery (day)	1.01±0.12	1.07±0.31	0.324

There is no significant difference in mean between both groups in terms of duration of the operation, gas insufflation time and days after surgery.

Table 4 **Analysis surgical difficulties and surgeon's experience level between the two groups.**

		Standard pressure group n (%)	Low pressure group n (%)	p-value
Difficulty of the operation	easy	38 (63.3 %)	32 (53.3%)	0.382
	medium-heavy	12 (20 %)	19 (31.7 %)	
	heavy	10 (16.7 %)	9 (15%)	
Surgeon's experience level	consultant	15 (25%)	18 (30%)	0.351
	fellow	10 (16.7%)	8 (13.3%)	
	resident	35 (58.3%)	34 (56.7%)	

There is no significant difference between both groups in terms of difficulty of the operation and surgeons experience level

Table 5 **Postoperative pain score (after 6h, 12h, 24h, 7 days) between the two groups.**

		Standard pressure group (median pain score)	Low pressure group (median pain score)	p-value
Time after surgery	6h	6	5	0.020
	12h	4	3	0.431
	24h	3	2	0.262
	7 days	1	0	0.283

The difference is significant between the two groups in pain score at the 6-hour post-operative time point with a p-value of $0.021 < 0.05$, a less significant difference was observed at other time points (p-value > 0.05)

Table 6 **Analysis of inflammatory markers (the morning before surgery and 24 h after surgery) between the two groups**.

Marker	Time	Standard pressure group		Low pressure group		p-value
		Count	Mean±SD	Count	Mean±SD	
WBC (10^9 cells/mm)	Pre op	47	7.85 ±2.26	48	7.52±2.4	0.49
	Post op	47	10.39±2.9	48	10.0±4.1	0.62
	ΔWBC	47	2.53±2.37	48	2.49±3.64	0.96
Platelet (10^9 g/L)	Pre op	47	275.91±77.41	48	284.167±69.94	0.58
	Post op	47	269.94±81.65	48	271.188±88.38	0.94
	ΔPlatelet	47	-5.98±35.63	48	-12.979±53.48	0.45
ESR (mm/hr)	Pre op	43	18.98±18.1	43	16.45±12.1	0.46
	Post op	43	22.93±16.36	42	20.66±13.74	0.49
	ΔSE	43	3.95±8.65	43	3.65±7.38	0.86
CRP (mg/L)	Pre op	47	6.41±8.135	47	4.5±5.51	0.18
	Post op	47	23.1±39.45	47	18.85±15.57	0.49
	ΔCRP	47	16.68±38.08	47	14.355±13.84	0.69
Albumin (g/dL)	Pre op	48	4.512±0.28	47	4.42±0.333	0.144
	Post op	48	4.25±0.31	47	4.16±0.34	0.186
	ΔAlb	48	-0.265±0.257	47	-0.26±3.461	0.934
IL-6 (pg/mL)	Pre op	32	2.88±9.4	45	24.82±118	0.02
	Post op	32	3.89±9.81	45	1.90±2.01	0.03
	ΔIL-6	32	1.079±5.55	45	-22.223± 125.4	0.025

Significant difference observed in inflammatory marker level IL-6 (pre op, post op, ΔIL-6).

DISCUSSION

To date, there is no consensus on the standard pressure during laparoscopic surgery, but most surgical societies agree on "the lowest intra-abdominal pressure that allows adequate exposure of the operative field, rather than routine pressure". Low-pressure pneumoperitoneum, defined in the literature as a pressure of 10 mmHg or less, avoids the detrimental physiological effects of intra-abdominal gas insufflation. In our study, the majority of operations were performed by inexperienced surgeons (senior residents), and the distribution of operations performed by residents was not statistically significant between these two groups. We found no correlation between the difficulty of the operation and the level of experience of the operator, indicating that low-pressure pneumoperitoneum is feasible even in the hands of less experienced surgeons. Regarding the safety of low-pressure pneumoperitoneum, Mandal A, et al. found no statistically significant difference in terms of surgical difficulty, conversion rate, or postoperative complication rate of low-pressure pneumoperitoneum when performed by more experienced surgeons (3). The operative field is not compromised at lower pneumoperitoneum pressures. Hua J, et al. had similar results. Even our study reflects similar results in the hands of less experienced surgeons (4). Mahajan S, et al. proposed standardizing laparoscopic low-pressure cholecystectomy in day surgery, as they found the procedure to be safe and feasible, with no statistically significant difference compared with standard-pressure pneumoperitoneum in terms of adequacy of the surgical field, contact of the parietal peritoneum to the underlying viscera during secondary port placement, operative duration, complication rate, and difficulty of the operation (5). In this study, the total operative time, insufflation time, and total hospital stay were similar in both groups. None of the patients had a major intraoperative complication, and the 30-day mortality rate was zero in both groups. The benefits of low-pressure pneumoperitoneum surgery have been reported by many to result in significant reductions in postoperative pain and shoulder pain after laparoscopic cholecystectomy among patients undergoing low-pressure pneumoperitoneum surgery.

However, a recent study by Chang W, et al., reported conflicting results with no significant difference in postoperative pain between low-pressure and very low-pressure pneumoperitoneum surgeries (6). Moro ET, et al., reported similar results (7). Our pain results support the additional benefit of low-pressure pneumoperitoneum in reducing postoperative pain perception; our four selected pain variables showed a lower mean pain score in the low-pressure group, with a significant difference observed at 6 hours after surgery. The total number of postoperative analgesics administered was lower in the low-pressure group, but we could not find a significant difference. Some other clinical trials have also shown significant reductions in postoperative nausea, early resumption of oral feeding, and hospital stay in the low-pressure groups. In a study of the hemodynamic effects of low-pressure pneumoperitoneum, heart rate, mean arterial pressure, and end-tidal carbon dioxide were found to vary intraoperatively. There have been conflicting results regarding the effects of low-pressure pneumoperitoneum on these parameters. Tripathi V, et al., found an increase in heart rate in the standard pressure group after 10 minutes of surgery that was evident in the low-pressure group, but this difference was not statistically significant (8). Singh et al. demonstrated a significant difference after 10 minutes of surgery, and a significant difference in systolic and diastolic blood pressure after 30 minutes of surgery. However, a study by Kanwer DB, et al., found no statistical difference in systolic or diastolic blood pressure (9). The use of low-pressure pneumoperitoneum was also demonstrated to have a reduced effect on liver injury, and a significant reduction in liver enzyme elevations. Neogi P, et al., could observe an increase in bilirubin and liver enzymes 24 h after surgery in the standard pressure pneumoperitoneum that was not demonstrated in the low pressure group, which recommends the use of low pressure pneumoperitoneum in patients with impaired liver function (10). Our clinical trial did not study such effects. The effect on the immune response has been reported in only a few studies, our study focused on inflammatory mediators affected by stress after surgery. Schietroma M, et al., observed a significant decrease in interleukins IL-1, IL-6 and CRP (11). Basgul E, et al., observed a significantly lower increase in IL-6 up to 24 h after surgery, but still higher levels of IL-2 during low pressure pneumoperitoneum. On the contrary, some other studies failed to detect a benefit (12). We were able to detect a reduction in 6 out of 6 inflammatory markers in the low-pressure group, and the statistically significant difference was in IL-6 values.

CONCLUSION

Laparoscopic cholecystectomy at lower pneumoperitoneum pressures is associated with less postoperative pain and a smaller increase in inflammatory markers. It has been previously demonstrated that the rise of intra-abdominal pressures and prolonged exposure to such pressures can produce changes in the cardiovascular and pulmonary dynamic which, though potentially well tolerated in the majority of healthy patients with adequate cardiopulmonary reserve, may be less well tolerated when cardiopulmonary reserve is poor. This may help in smooth recovery and less post-operative problems.

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Material Compensation and Its Impact on Work Efficiency of Professionals in Primary, Secondary and Tertiary Level of Healthcare

Utjecaj materijalnih kompenzacija na radnu efikasnost zdravstvenih profesionalaca zaposlenih na primarnom, sekundarnom i tercijarnom nivou zdravstvene zaštite

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ABSTRACT

Introduction: material compensation for employees is a part of business strategy that primarily depends on available resources and, subsequently, on the organization's business policy. Salaries, as a form of material compensation, represent the most concrete, significant, and stimulating form of recognition for an individual's work and performance. Aim: to assess the level of employee satisfaction with material compensation for work and its impact on the work efficiency of healthcare professionals. Materials and methods: the study was conducted in the following healthcare institutions: For the primary level - Public Primary Health Centers of Sarajevo; 50 doctors, 100 nurses - a total of 150 respondents. For the secondary level - General Hospital "Prim. dr. Abdulah Nakaš" Sarajevo; 50 doctors, 100 nurses - a total of 150 respondents. For the tertiary level - Clinical Center of Sarajevo; 50 doctors, 100 nurses - a total of 150 respondents. The total number of respondents from the mentioned health institutions is 450, while the research was conducted with the approval of the health institutions. The inclusion criteria are as follows; respondents are doctors (specialists and doctors in specialization), nurses, who are employed in the mentioned health institutions. The implementation of this study was carried out on a voluntary basis by employees, anonymously. The research was conducted in 2018 with the approval of the ethics committees of the respective healthcare institutions. The study used a cross-sectional, comparative, analytical research design. It utilized a modified, combined, closed-and open-ended questionnaire based on the Likert scale (1–5), where 1 represented strong disagreement and 5 indicated complete agreement with the given statement. Results: the findings indicate a positive correlation between the different examined groups and significant similarities in the opinions of respondents across various levels of healthcare. According to the participants, there is pronounced dissatisfaction with the level of material compensation for work. Conclusion: employees are dissatisfied with their material compensation and believe it should be immediately revised and adjusted. No incentives exist for better performance, advanced knowledge, or increased effort.

Keywords: material compensation, work motivation, healthcare professionals, work efficiency

SAŽETAK

Uvod: materijalno nagrađivanje zaposlenih je dio poslovne strategije, koji zavisi prije svega od mogućnosti, a zatim i poslovne politike same organizacije. Materijalne nagrade zaposlenima izražene u vidu plate su najkonkretniji, vrlo važan i stimulativan oblik priznanja nečijeg rada i radnog učinka. Cilj: evidentirati stepen zadovoljstva zaposlenih samaterijalnom kompenzacijom za rad i njen utjecaj na radnu efikasnost zdravstvenih profesionalaca. Materijali i metode istraživanja: Ispitivanje je provedeno u slijedećim zdravstvenim ustanovama: Za primarni nivo - JU Dom zdravlja Sarajevo; ljekara 50, medicinskih sestara 100 (VSS/VSŠ i SSS), ukupno 150 ispitanika. Za sekundarni nivo - Opća bolnica "Prim. dr. Abdulah Nakaš" Sarajevo; ljekara 50, medicinskih sestara 100 (VSS/VSŠ i SSS), ukupno 150 ispitanika. Za tercijarni nivo - Klinički centar Sarajevo; ljekara 50, medicinskih sestara 100(VSS/VSŠ i SSS), ukupno 150 ispitanika. Ukupan broj iz navedenih zdravstvenih ustanova je 450 ispitanika, dok je istraživanje sprovedeno uz odobrenje zdravstvenih ustanova. Kriteriji za uključenje su slijedeći; ispitanici su ljekari (specijaliste i ljekari na specijalizaciji), medicinske sestre (VSS/VSŠ i SSS), koji su zaposleni u navedenim zdravstvenim ustanovama. Realizacije ove studije je na dobrovoljnoj bazi zaposlenika, anonimno provedena. Istraživanje je realizirano 2018 godine u navedenim, uz odobrenje etičkih komiteta zdravstvenih ustanova. Metoda istraživanja je presječna (cross-sectional) komparativna, analitička studija. Za predviđeno istraživanje korišten je modifikovano kombinovani zatvoreno-otvorenog tipa upitnik prema Likertovom modelu sa skalom od 1-5, pri čemu 1- izrazita negacija; 5- potpuno slaganje sa postavljenom tvrdnjom. Rezultati: pokazuju pozitivnu koleraciju između različitih ispitivanih grupa, kao i velike sličnosti u stavovima ispitanika sa različitih nivoa ZZ. Prema mišljenju ispitanika postoji izrazito nezadovoljstvo sa visinom materijalnih kompenzacija za rad. Zaključak: zaposleni nisu zadovoljni materijalnim nagrađivanjem i smatraju da ga treba odmah mijenjati i prilagođavati, nema stimulacija za bolji rad, veće znanje i zalaganje.

Ključne riječi: materijalna kompenzacija, motivacija za rad, zdravstveni profesionalci, efikasnost na radu

INTRODUCTION

Every healthcare organization implements different strategies for the material compensation of employees to create a positive effect on motivation for many people. However, when it comes to individual motivation, there is no automatic correlation between higher salary →greater motivation →increased work performance.

Material compensation for healthcare employees is realized through:

a) Direct financial benefits, which employees receive in monetary form, such as salaries.
b) Indirect financial benefits, which employees do not receive directly as part of their salary but contribute to their overall financial well-being.

The second category includes a range of benefits such as health and pension insurance, meal allowances, life insurance, paid leave, and vacation days.

Motivation is essential to achieve high standard of quality of work, for encouraging creativity and innovation, for the professional development of employees and their retention in the company. Promotions, status symbols, recognition, salaries and other material compensations are visible mechanisms for allocating specific rewards and valuing work within the policies and practices of each individual organization (1).

The relationship between work motivation, engagement, and employee identification was explored by Galetić, who concluded that employees primarily require monetary compensation or another form of remuneration with financial value based on their work performance (2).

In reward systems, financial compensation that employees can receive consists of:

- Salary systems and other material benefits (meal allowances, transportation subsidies).
- Individual rewards and bonuses for exceptional work contributions.
- Incentive programs, including one-time, group, or special bonuses.
- Employee profit-sharing is linked to the organization's financial performance.
- Salary increases adjusted to cost-of-living changes (2).

For a compensation system to be effective and stimulating, it must meet the following criteria:

- Simplicity - The system's rules should be clear, concise, and understandable to all employees.
- Specificity - Employees must clearly understand what is expected of them, the concrete and specific goals, and which work procedures apply to everyone equally.
- Achievability - Employees must have the opportunity to reach their goals and fully express their professional and creative potential.
- Measurability - Measurable goals are essential for both individual and organizational incentives.
- Fairness - Equal and fair treatment for all employees is a crucial aspect of any reward system.

The changing dynamics of modern business are pushing organizations toward new approaches to work evaluation and salary determination. The focus is shifting toward skills, knowledge, abilities, and the capacity to perform multiple tasks. In this system, the base salary is determined by the number of skills employees have mastered, their knowledge, and the tasks they can perform. The more an employee learns, the more valuable they become, increasing their earning potential accordingly.

Many well-known companies, such as Project and General Motors, are increasingly adopting skill-and knowledge-based salary systems. Recent studies show that implementing this model in 70%-80% of cases leads to higher job satisfaction, improved work quality, lower operational costs, and reduced employee turnover.

This system offers numerous advantages, including a better understanding of job roles, greater opportunity for innovation and work improvement suggestions, utilization of diverse employee skills, flexibility and rotation, better comprehension of work processes, and increased job satisfaction. However, performance-based compensation has both positive and negative aspects. While it can encourage individual excellence, it may also discourage teamwork. On the other hand, failing to reward creative and high-performing individuals adequately can lead to demoralization and high attrition rates, as the best employees leave the organization. Therefore, finding the right balance between individual and group incentives is essential (3).

Performance-based salary models

Direct supervisors should conduct performance evaluations of employees at least once a year. Work assessment does not impact salary levels in the current system, where healthcare professionals' salaries are determined by working hours rather than performance. Instead, it identifies skill gaps and creates training plans for further education. In the current compensation system, performance evaluation does not provide an opportunity for better financial compensation - meaning that employees earn the same regardless of how much effort they put in.

However, a well-designed performance-based compensation system offers multiple benefits:

a) Establishing high work standards that demand excellence rather than mediocrity.
b) Developing a structured performance evaluation system with multiple evaluators and clear criteria.
c) Training managers in performance assessment skills, enabling them to manage low performance and drive improvement
d) Strongly linking rewards to performance, with more frequent evaluations (semi-annual assessments) directly affecting salary increases or reductions.

A key condition for a motivational performance-based salary system is that a significant portion of earnings (around 50%) should depend on performance. This approach establishes a clear connection between work effort and salary. The purpose of such a system is to encourage high-quality work, professional development, and the acquisition of skills needed for efficient task execution.

Modern reward systems face the dilemma of individual vs. team-based incentives. On the one hand, modern technology and work conditions increasingly require teamwork. On the other hand, psychological research suggests that individual motivation remains crucial (4).

Healthcare organizations often need to develop programs that enhance work processes by improving work quality, reducing absenteeism, optimizing work hours, increasing efficiency, and lowering material costs (5).

To achieve this, flexible incentive programs can be implemented, allowing employees to choose their preferred type of reward whether additional days off or financial bonuses.

Group Incentive Systems

Modern practice applies various forms of material rewards and financial participation for employees at all organizational levels. The common goal of all these systems is to align individual employee interests with broader organizational objectives. New systems are being developed while existing alternative reward systems are being modified. The most well-known among them include:

Employee Profit Sharing-Gainsharing is a formal program that allows employees to participate financially in the profits generated from increased productivity. These systems "share responsibilities and rewards for organizational improvements among all employees."

Employees' direct participation in material gains results from:
- Cost savings and reduction in labour expenses,
- Increased added value is achieved through greater employee engagement.

From a motivational perspective, an employee profit-sharing system aims to (6):
- Improve the quality of work life and operational efficiency,
- Increase motivation and job satisfaction,
- Encourage employees to participate in problem-solving actively,
- Enhance communication and collaboration within departments.

The Scanlon Plan is the most well-known system of performance-based rewards for employees. The creator, renowned MIT professor Joseph Scanlon, designed this program to "save companies" by fostering genuine cooperation between management and employees and leveraging employees' intellectual abilities, knowledge, and experience through active participation in problem-solving.

The core principles of this system include:
- employees receive the full savings from cost reduction and increased production.
- bonuses are distributed to all employees in the organization.
- a group-based reward system-there is no measurement of individual performance and contribution.
- joint committees, composed of employee representatives (unions) and management, oversee all cost savings and expense reduction suggestions.

Today, this incentive system is widely accepted and implemented in many companies worldwide. Scanlon's idea was to distribute the total savings equally among employees, but in many organizations, the savings are split, with 75% allocated to employees and 25% retained by the organization.

Companies implementing this system see increased work efficiency and quality and a significant rise in employee earnings. Moreover, a positive work atmosphere is created, where employees actively participate in solving organizational challenges by providing suggestions and driving innovation. Employee involvement in decision-making fosters a sense of personal contribution and the importance of everyone within the organization.

Employee Profit Sharing is a widely adopted method for incentivizing employees through shared profits (7). Henri Fayol developed this concept as part of his general management theory. Profit sharing is a direct form of financial participation in the company's overall success, reflected in its profits. Organizations allocate a portion of their planned profits (10%-30%) for distribution to employees. This distribution is separate from the regular salary system and is provided as follows:
- once or twice a year.
- all employees participate in the distribution.
- the basis for participation is employment in the company.

Organizations implement this system for several reasons:
- It ensures group incentives for both personal and organizational success,
- It strengthens employees' sense of security and identification with the organization,
- It establishes a flexible reward structure,
- It educates and informs employees about the foundations of business success,
- It attracts and retains top professionals.

Since this system is separate from regular salaries, it is distributed only when the company performs well and has the financial capacity to do so. These systems are becoming part of collective agreements and contracts between employers and employees.

Employee Ownership Participation (Stock Sharing) refers to acquiring shares based on generated profit. In addition to stock option programs, savings programs have also been developed, allowing employees to purchase shares after a certain period, exempt from income tax (8).

Benefits

Benefits are various forms of compensation that directly impact employees' economic well-being during and after their employment. Security and Health Benefits: Pension insurance, health insurance, life insurance, compensation for illness or accidents, sick leave, unemployment benefits, severance pay, and more.

Paid Time Off - Leave Benefits: Holidays, justified absences, paid leaves, appeal procedures, negotiations, and paid time for professional development and education.

Employee Services: Scholarships and financial aid for education, employee loans, meal services, company cars, professional attire, legal services, savings programs, childcare, and eldercare transportation, various service awards, tenure-based and special occasion bonuses, recreation and wellness programs, social activities, relocation and transfer expenses, discounts on company products, sales of decommissioned equipment, holiday bonuses, and parking. Security and health benefits are the most important, focusing on employees' economic and health protection and safety throughout their careers and retirement. This "side money" represents the largest source of capital in the American and global capital markets, accounting for one-quarter of corporate capital. Leading global companies offer their employees-especially highly skilled professionals working in mentally demanding jobs opportunities to take paid breaks for a specific period. These paid leaves can be short- or long-term (such as eight weeks or up to a year for professors conducting research). Studies have shown that this benefit is highly valued (9).

AIM

The aim of the research was to assess employee satisfaction with material compensation for work and its impact on the work efficiency of healthcare professionals**.**

MATERIALS AND METHODS

The study was conducted in the following healthcare institutions: For the primary level - Public Primary Health Centers of Sarajevo; 50 doctors, 100 nurses - a total of 150 respondents. For the secondary level - General Hospital "Prim. dr. Abdulah Nakaš" Sarajevo; 50 doctors, 100 nurses - a total of 150 respondents. For the tertiary level - Clinical Center of Sarajevo; 50 doctors, 100 nurses - a total of 150 respondents. The total number of respondents from the mentioned health institutions is 450, while the research was conducted with the approval of the health institutions.

Inclusion criteria for the study: participants are physicians (specialists and resident physicians) and nurses (Bachelor's/Master's and Secondary School of Nursing) employed in the mentioned healthcare institutions. The implementation of this study was carried out on a voluntary basis by employees, anonymously.

Exclusion criteria from the study: failure to meet the predetermined criteria for inclusion.

The research was conducted in 2018 with the approval of the ethics committees of the respective healthcare institutions. The study used a cross-sectional, comparative, analytical research design.

Research methods

The research is a cross-sectional, comparative, analytical study. Research instruments: a modified combined closed-open type questionnaire according to the Likert model was used for the planned research. The questionnaire contained thirty statements related to factors affecting work efficiency: material rewards, non-material motivational strategies, employee education planning, personal career development, stress at the workplace. Answers to the posed statements are on a scale from 1 to 5, where 1 is strong denial, 2 is denial of the statement, 3 is undecided, 4 is agreement with the statement, and 5 is complete agreement.

At the end of the questionnaire, room is left for open remarks and suggestions, so that participants can, after seeing the statements in the questionnaire, make their own suggestions on how things could be improved. All surveys were in the form of anonymous questionnaires.

Ethical aspect of the research - the study was conducted following the basic principles of the Helsinki Declaration (last revision 2008). The realization of this study was voluntary and conducted anonymously by employees. Participants' data will not be entered into the questionnaire.

RESULTS

Participants are doctors (specialists and residents) and nurses (Bachelor's/Master's and Secondary School of Nursing) of various ages and genders, regardless of their length of work experience and job position. Table 1. shows the structure of participants according to professional qualifications.

Table 1 **Demographic characteristics of participants: profession affiliation and professional qualifications.**

	Doctors	Registered Nurses with a bachelor's degree	Registered Nurses with a Highschool Diploma	Total
Primary Health Care	50	21	79	150
Secondary Health Care	50	19	81	150
Tertiary Health Care	50	44	56	150
Total	150	84	216	450

Table 2 **Respondents' opinion on the amount of monthly earnings: „A small but regular salary is good ".**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	56	37.3	39	26.0	16	10.6	21	14.0	18	12,0	2.37	1.41
Secondary Health Care	53	35.3	29	19.3	23	15.3	34	22.6	11	7.3	2.47	1.36
Tertiary Health Care	44	29.3	36	24.0	24	16.0	33	22.0	13	8.6	2.56	1.34
Total	**153**	**34.0**	**104**	**23.1**	**63**	**14.0**	**88**	**19. 5**	**42**	**9.3**	**450= 100%**	

(x2=10.28, p>.05)

The chi-square test of independence did not reveal a statistically significant difference between the three groups regarding respondents' attitudes toward the statement: "A small but regular salary is good" ($X^2(8, n=450) = 10.28, p = 0.2457$). 28.8% of respondents agree with the statement, while the rest express their disagreement.There is no statistically significant difference in respondents' opinions on the given statement ($X^2=10.28, p>.05$).

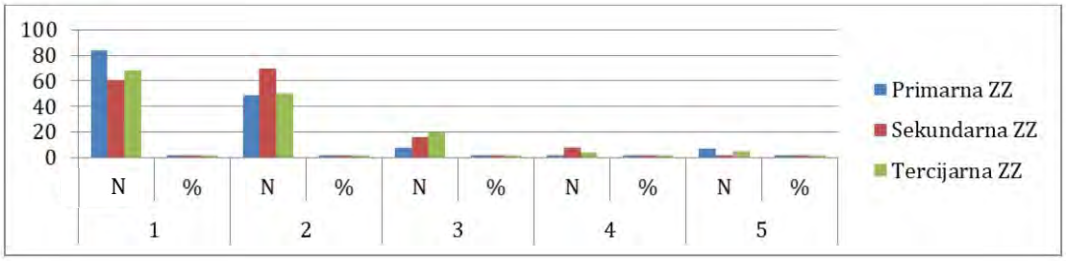

Figure 1 **Respondents' attitude about financial compensation of health care professionals**.

Table 3 **Statement: „The company adequately values your work".**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	107	68.0	26	17.3	8	5.3	9	6.0	0	0.0	1.46	0.84
Secondary Health Care	68	45.3	50	33.3	19	12.6	11	7.3	2	1.3	1.86	0.99
Tertiary Health Care	73	48,6	55	36,6	17	11,3	4	2,6	1	0,6	1,7	0,83
Total	**248**	**55.1**	**131**	**29.1**	**44**	**9.7**	**24**	**5.3**	**3**	**2.0**	450=100%	

(x2=30.30, p<0.05)

The chi-square test of independence revealed a statistically significant difference between the three groups regarding respondents' attitudes toward the statement: "The company adequately values your work" ($X^2(8, n=450) = 30.30, p=0.0019$). Only 7.3% of respondents agree with this statement.There is a statistically significant difference in respondents' attitudes toward the given statement ($X^2 = 30.30, p < 0.05$).

Table 4 **Statement: „Increased effort and work lead to higher earnings".**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	110	73.3	27	18.0	5	3.3	6	4.0	2	1.3	1.46	0.84
Secondary Health Care	71	47.3	54	36.0	11	7.3	10	6.6	4	2.6	1.86	0.99
Tertiary Health Care	60	40.0	54	36.0	14	9.3	16	10.6	6	4.0	1.7	0.83
Total	**241**	**53.3**	**135**	**30.0**	**30**	**6.6**	**32**	**7.1**	**12**	**2.6**	**450 = 100%**	

(x2=38.94, p<0.05)

The chi-square test of independence showed a statistically significant difference between the three groups regarding respondents' attitudes toward the statement: "When I work more, I earn more" ($X^2(8, n=450) = 38.94, p < 0.00001$). The most incredible statistically significant difference in attitudes between the groups was observed between the PZZ and TZZ groups ($X^2(4, n=300) = 34.515, p < 0.00001$). 83,3% of respondents strongly disagree with the statement. There is a statistically significant difference in respondents' attitudes toward the given statement ($X^2 = 38.94, p < 0.05$).

Table 5 **Display of Results on "Employee Material Compensation Strategies".**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	388	43.1	182	20.2	97	10.7	95	10.5	138	15.3	2.35	1.49
Secondary Health Care	267	29.6	230	25.5	138	15.3	164	18.2	101	11.2	2.56	1.37
Tertiary Health Care	247	27.4	233	25.8	140	15.5	167	18.5	113	12.5	2.63	1.38
Total	**902**	**33.4**	**645**	**23.8**	**375**	**13.8**	**426**	**15.7**	**352**	**13.0**	2700=100%	

(x2=85.20, p<0.05)

The chi-square test of independence revealed a statistically significant difference between the three groups regarding respondents' attitudes toward the topic "Material Reward Strategy" ($X^2(8, n=2700) = 85.20, p < 0.00001$). There is a statistically significant difference in respondents' attitudes toward the statements related to the factor-material reward strategies ($X^2 = 85.20, p < 0.05$).

Table 6 **Statement: „The reward system is fair and motivational".**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	69	46,0	28	18.6	23	15.3	15	10.0	15	10.0	2.35	1.49
Secondary Health Care	34	22.6	35	23.3	30	20.0	32	21.3	19	12.6	2.56	1.37
Tertiary Health Care	36	24.0	50	33.3	21	14.0	23	15.3	20	13.3	2.63	1.38
Total	**139**	**30.8**	**13**	**25.1**	**74**	**16.4**	**70**	**15.5**	**54**	**12.0**	**450= 100%**	

(x2=32.17, p<0.05)

The chi-square test of independence revealed a statistically significant difference between the three groups regarding respondents' attitudes toward the statement: "The reward system is fair and motivational" ($X^2(8, n=450) = 32.17, p = 0.000087$). Only 27.5% of respondents agree with the statement, while the other 72.5% strongly disagree. There is a statistically significant difference in respondents' attitudes toward the given statement ($X^2 = 32.17, p < 0.05$).

Table 7 **Statement: „The reward system needs to be changed immediately ".**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	11	7.3	10	6.6	14	9.3	30	20.0	85	56.6	4.12	1.26
Secondary Health Care	14	9.3	17	11.3	23	15.3	44	29.3	52	34.6	3.68	1.31
Tertiary Health Care	12	8.0	11	7.3	22	14.6	55	36.0	50	33.3	3.8	1.21
Total	**37**	**8.2**	**38**	**8.4**	**59**	**13.1**	**129**	**28.6**	**187**	**41.5**	**450= 100%**	

(x2=24.81, p<0.05)

The chi-square test of independence revealed a statistically significant difference between the three groups regarding respondents' attitudes toward the statement: "The reward system needs to be changed immediately" ($X^2(8, n=450) = 24.81, p = 0.001671$). 83,4% of respondents strongly agree with the statement. There is a statistically significant difference in respondents' attitudes toward the given statement ($X^2 = 24.81, p < 0.05$).

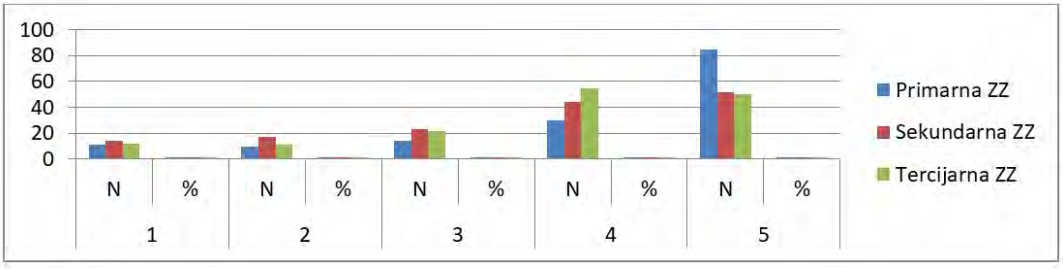

Figure 2 **Respondents' opinion on the existing employee reward system. The reward system should be changed immediately**.

DISCUSSION

Material compensation is considered very important by healthcare professionals, as it is a prerequisite for a normal life and family security. The statement "a small but regular salary is good" caused strong dissatisfaction in 57.1% of participants. Health professionals believe that society does not value their work adequately, as reflected in 84.1% of responses. Material compensation is causally related to work motivation and performance. Employees feel that an increase in effort and work does not affect their salary (83.3%), the salary remains fixed on work performance. More than two-thirds of respondents (71.1%) believe the current reward system is not adequate, fair, or motivational. Material reward was a factor that negatively impacted work motivation, according to this research.

Healthcare organizations must apply various material reward strategies to generate positive work effects that motivate many people. The research on the impact of factors-Material Reward Strategies on the work efficiency of healthcare professionals-showed that the chi-square test of independence revealed a statistically significant difference between all three groups in respondents' attitudes ($X^2 = 85.20, p < 0.05$). The employee payment system is based on working hours, not work performance. This means that everyone has the same salary within a certain category regardless of the workload, amount of work, knowledge and skills, creativity, or individual contribution. A large percentage of disagreement is expressed by 83.3%. The amount of material compensation, in the form of salary and other salary supplements, in the healthcare system often does not depend on the strategic management of healthcare institutions. The healthcare sector's financing relies on the Health Insurance Fund (ZZO) and the Ministry of Health.

Salaries, as confirmed by this research, are the most common financial motivator for healthcare employees, aligning with the results of Tomas' study (10). If management "forgets" to stimulate a working organization that produces extremely high work results, it has missed the opportunity to demonstrate, through good reward practices, the difference between a good and a bad organization. The study revealed that the material reward segment, job security, health and pension insurance, and other benefits related to the salary are very important for the professions of doctors and nurses in all surveyed centers.

IvanovA published a research paper in 2019 entitled "Motivation of employees in healthcare" where he agreed thatnurses want to be able to apply their acquired knowledge and skills in clinical practice and their work with patients (11).

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Contrary to the findings of this study, Thomas S (10) did not find that employees in healthcare organizations expressed interest in other forms of compensation. Healthcare professionals are dissatisfied with material compensation. The reward system is inadequate, and 87.6% of respondents believe it should be changed immediately.

CONCLUSION

Healthcare professionals are not satisfied with the material reward they receive for their work.They believe that their profession is not well valued by society. Material rewards for employees need to be adjusted according to the complexityof their work and job requirements (in terms of the required knowledge and skills, and the amount of work they perform). The collective labouragreement that is currently in effect equalizes all systems in the healthcare sector.The salary of doctors and nurses is equal for those employed in primary healthcare facilities and in a subspecialty branch at the tertiary level of healthcare. The reward system is unfair, unmotivating, and should be changed immediately. The reward system is inadequate at all levels of healthcare, however the need for its adjustment is more prominent at the secondary and tertiary levels. Healthcare professionals must be paid adequately. Otherwise, they will be forced to look for employment in foreign countries, which can collapse our entire healthcare system.

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Rates and Risk Factors for Hospital Readmission in Term Newborns

Stopa i faktori rizika za rehospitalizaciju u terminske novorođenčadi

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ABSTRACT

Introduction: rehospitalization of newborns is defined as hospitalization within 28 days of discharge from the maternity hospital. It represents an emotional, social and financial burden on the family and the health system. Aim: to analyze the rate and outcome of neonatal rehospitalizations in term newborns and their association with neonatal and maternal risk factors. Material and methods: a retrospective cohort study was performed by reviewing the medical records of 51 term newborns admitted to the Pediatric Clinic, Clinical Center University of Sarajevo from June 2023 to June 2024. Results: the neonatal readmission rate during the study period was 1.3 %. The most common causes for readmission were jaudince (51%), perinatal infection (39.2%), and bronchiolitis (9.8%). The mean age at readmittion was X8.9±7.6 days of life. According to the chi-square test, only body weight at admission had a statistically significant association p<0.001 from which we can conclude that newborns with a low birth weight or low postnatal weight gain have increased risk of rehospitalization. Conclusion: the most common causes of rehospitalization of term newborns were hyperbilirubinemia and early neonatal infection. The evaluation of factors associated with readmission and follow-up after discharge may reduce the readmission rate.

Keywords: neonatal rehospitalization, newborn, causes of rehospitalization

SAŽETAK

Uvod: rehospitalizacija novorođenčadi definira se kao hospitalizacija unutar 28 dana od otpusta iz porodilišta. Predstavlja emocionalno, socijalno i financijsko opterećenje za obitelj i zdravstveni sistem. Cilj: analizirati stopu i ishod neonatalnih rehospitalizacija u terminske novorođenčadi i njihovu povezanost s neonatalnim i majčinim faktorima rizika. Materijal i metode: retrospektivna kohortna studija provedena je pregledom medicinske dokumentacije 51 terminskog novorođenčeta primljenog na Pedijatrijsku kliniku Kliničkog centra Univerziteta u Sarajevu od juna 2023. do juna 2024. Rezultati: stopa ponovnog prijema novorođenčadi tokom perioda istraživanja bila je 1,3 %. Najčešći uzroci rehospitalizacije bili su žutica (51%), perinatalna infekcija (39.2%) i bronhiolitis (9.8%). Prosječna dob pri rehospitalizaciji bila je 8,9±7,6 dana života. Prema hi-kvadrat testu samo je tjelesna težina u momentu prijema, imala statistički značajnu povezanost p<0,001, iz čega možemo zaključiti da novorođenčad niske porođajne težine ili malog postnatalnog dobitka na težini imaju povećan rizik od ponovne hospitalizacije. Zaključak: najčešći uzroci rehospitalizacije terminske novorođenčadi bili su hiperbilirubinemija i rana neonatalna infekcija. Procjena faktora povezanih s rehospitalizacijom i praćenje nakon otpusta mogu smanjiti stopu rehospitalizacije.

Ključne riječi: neonatalna rehospitalizacija, novorođenče, uzroci

INTRODUCTION

A better understanding of the probability, timing and prediction of rehospitalization amongst newborns could help improve outcomes and reduce the burden on the family and the health system. Rehospitalization of newborns is defined as hospitalization within 28 days of discharge from the maternity ward (1).

Before discharge from the maternity ward, various tests and examinations are performed to assess the newborn's readiness for discharge. Still, the readmission may occur. Therefore, identifying the associated maternal and neonatal risk factors is essential.

Neonatal jaundice is the most common condition that requires medical attention and hospital readmission in newborns and it is a clinical manifestation of elevated total serum bilirubin.

Neonatal early-onset sepsis (EOS) is defined as blood or cerebrospinal fluid culture-proven bacterial infection of the newborn occurring in the first 7 days of life.

A high percentage of rehospitalization is a negative indicator of the quality of health care (2).

The rate of rehospitalization during the neonatal period ranges from <1% in the most developed countries to near 10% in countries with an underdeveloped health system (3).

Previous studies have primarily investigated the incidence and causes of neonatal readmission, but with little focus on maternal and neonatal risk factors associated with readmission (4,5).

AIM

The aim of this study was to analyse the maternal and neonatal factors that would increase the risk of readmission and readmission outcome.

MATERIALS AND METHODS

We conducted a retrospective cohort study and reviewed of all medical history of term newborns from the Canton Sarajevo, rehospitalized to the Department of Neonatology of the Pediatric Clinic of the Clinical Center University of Sarajevo in the period of one year (June 1, 2023 - June 1, 2024).

All full-term newborns who were rehospitalized within 28 days of life, after discharge from the maternity ward, due to the development of a pathological condition were analyzed.

Newborns who were immediately transferred to the Department of Neonatal Intensive Care after birth, as well as newborns admitted to the Department of Neonatology, as a transfer from other cantons, were not included in the research. The following parameters were monitored in the newborns: sex, birth weight, body weight at admission, postnatal weight gain, age at admission, feeding model (breastfeeding/formula feeding) and diagnosis at admission.

We monitored the following parameters in mothers: mode of delivery, number of deliveries and comorbidities. The data were taken from the patient's medical history. The Chi-square (X^2) test was used for testing the statistical significance. The results are shown in number and relative frequency (%). P value of statistical significance is shown as $p<0.001$.

Salaries, as confirmed by this research, are the most common financial motivator for healthcare employees, aligning with the results of Tomas' study (10). If management "forgets" to stimulate a working organization that produces extremely high work results, it has missed the opportunity to demonstrate, through good reward practices, the difference between a good and a bad organization. The study revealed that the material reward segment, job security, health and pension insurance, and other benefits related to the salary are very important for the professions of doctors and nurses in all surveyed centers.

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Contrary to the findings of this study, Thomas S (10) did not find that employees in healthcare organizations expressed interest in other forms of compensation. Healthcare professionals are dissatisfied with material compensation. The reward system is inadequate, and 87.6% of respondents believe it should be changed immediately.

RESULTS

Out of 4089 newborns born in the Canton Sarajevo during the study period, 51 (1.25%) were readmitted within 28 days. Out of the readmitted newborns, 56.9% (n= 29) were males, 64.7% (n=33) were delivered vaginally, 94.1% (n=48) were singletons, 51% (n=26) were exclusively breastfed. Thirty newborns (58.8%) were readmitted within 7 days after initial discharge, whereas 21 (41.2%) were readmitted more than 7 days following discharge from maternity hospital. The mean age at readmission was 8.8±7,6 days of life. The majority of the mothers were multiparous 62.7% (n=32). The most common comorbidities among the mothers were thyroid related disorders (17.6%), diabetes (10.9%) and anemia (6.5%).

Body weight at admission varied from 2340-5160 (grams) with a mean value of 3297.94±563.23; body weight was divided into two groups, below the average of which there were 27 (52.9%) and 24 of them (47.1%) above the average (according to the WHO on the average value of the body weight of newborns). Body weight variations in children were related to a loss of 10% in 28 cases (54.9%) and an increase of 7% in 23 cases (45.1%).

Table 1 **Descriptive statistics of parameters in newborn (6).**

Newborn parameters	Variables	n	%
gender	male	29	56.9
	female	22	43.1
body weight	below the average	27	52.9
	abow the average	24	47.1
the time of reporting to the clinic	in the first half of the month	30	58.8
	in the second half of the month	21	41.2
the number of newborn	one	48	94.1
	two	3	5.9
Feeding model	breastfeed	26	51
	AMF	14	27.5
	combination	11	21.5
diagnosis	bronchiolitis	5	9.8
	hyperbilirubinemia	26	51
	early neonatal infection	20	39.2
body weight variation	loss 10%	28	54.9
	7% increase	23	45.1

Table 2 **Maternal parameters.**

Maternal parameters	Variables	n	%
mode of delivery	spontaneous	33	64.7
	S.C.	18	35.3
number of deliveries	primiparous	19	37.3
	multiparous	32	62.7
comorbidities	without	33	64.7
	with	18	35.3

Descriptive statistics of the mothers' parameters show the mode of delivery was spontaneous in 64.7% (33/51) and caesarean section in 35.3% (18/51). Out of total number of mothers 37.3 % (19/51) were primiparous (37.3%) and 62.7% (32/51) were multiparous women. The comorbidity was present in 18 mothers (35.3%).

Of the mentioned variables that we connected with the variable of time of presentation to the clinic, according to the chi-square test, only body weight at admission had a statistically significant association $p<0.001$ from which we can conclude that newborns with low birth weight or low postnatal weight gain have increased risk of rehospitalization.

The most common diagnosis at admission was hyperbilirubinaemia where phototherapy should be instituted, early neonatal infection and bronchiolitis.

Table 3 **The relationship between the variable time of presentation to the clinic and the variables of gender, body weight, number of newborns, diet, diagnosis and body weight variations.**

Parameter		the time of reporting to the clinic		
	Variables	The first half of month	The second half of month	*p*
gender	male	16	13	0.579
	female	14	8	
Body weight	bellow	23	4	<0.001
	above	7	17	
Number of newborns	one	28	20	0.776
	two	2	1	
Feeding model	breastfeeding	16	10	0.728
	AMF	7	7	
	combination	7	4	
diagnosis	bronchiolitis	2	3	0.106
	hyperbilirubinemia	19	7	
	early neonatal infection	9	11	
body weight variation	loss 10%	17	11	0.783
	7% increase	13	10	

Table 4 **The relationship between the occurrence of the disease and the variation in body weight and diet.**

Parameter		diagnosis			*p*
	Variables	bronchiolitis	hyperbilirubinemia	early neonatal infection	
body weight variation	loss 10%	0	21	7	<0.001
	7% increase	5	5	13	
Feeding model	breastfeeding	3	18	5	0.031
	AMF	1	6	7	
	combination	1	2	8	

After the analysis of the chi-square test, we proved that there is a statistically significant association with body weight variation p<0.001, which links a 10% loss of body weight in children with hyperbilirubinemia, while in bronchiolitis and early neonatal infection, a 7% increase is more common. Also, the feeding method has a significant connection with the diagnosis, in breastfeeding newborns hyperbilirubinemia is more frequent than other diagnoses p=0.031

Table 5 **The relationship between the mode of delivery in mothers and the presence of comorbidities and the number of deliveries.**

Parameter		mode of delivery		
	Variables	Spontaneous	S.C.	P
comorbidities	without	28	5	<0.001
	with	5	13	
Number of deliveries	primipareous	13	6	0.669
	multipareous	20	12	

According to the chi-square test, the analysis showed that there is a statistically significant relationship between the mode of delivery and the presence of comorbidities p<0.001. In Table 5, it can be seen that a greater number of spontaneous births occurred in mothers without the presence of comorbidities, while in mothers with the presence of comorbidities, the more common mode of delivery was caesarean section

DISCUSSION

Our analysis of medical records of 51 term newborns admitted in the one-year period (1 June 2023 to 1 June 2024) to the Department of Neonatology of the Pediatric Clinic, Clinical Center University of Sarajevo showed that birth weight at delivery and postnatal weight gain are the most important risk factors for early rehospitalization. The most common diagnosis at admission were hyperbilirubinaemia, early neonatal infection and bronchiolitis.

Previous research has shown that male newborns are more likely to be rehospitalized than female infants (7,8).

Although our observations concluded that gender does not have such a strong correlation in readmission, our findings are consistent with this assertion as there is a predominance of male infants in rehospitalization (56.9%), and fewer women (43.1%). According to the chi-square test, only body weight had a statistically significant association (p<0.001) from which we can conclude that children below the average weight are more likely to appear earlier than children with a body weight above the average (3.300 g).

Some studies show that lower birth weight has no effect on the readmission of newborns (8).

Most of the mothers of readmitted newborns were multiparous women. This could be a consequence of the neglect of raising awareness among multiparous women in contrast to primiparous women, assuming that they have prior knowledge and experience.

We proved that there is also a connection with body weight variation (p<0.001), which connects a 10% loss of body weight in children with hyperbilirubinemia. Also, the way of eating has a significant connection with the diagnosis, the most common diagnoses are hyperbilirubinemia in children who are breastfed compared to others diagnoses p=0.031.

Furthermore, we identified jaundice as the most common cause of rehospitalization.

Similarly, Alsulami M, et al., (3) also found that the most common cause of readmission was jaundice (38%), followed by genitourinary tract (11.4%) and gastrointestinal tract (11.3%).

In another single-center study conducted by Perme T, et al., jaundice was the most common readmission for full-term children after discharge from the maternity ward (4).

An increase in infant rehospitalization rates means an increase in health care costs, and therefore measures should be taken to prevent hospitalizations and reduce overall rates (9).

We believe that improving health care is not a big investment, and can bring great benefits not only to the system, children and families, but also to the whole society.

CONCLUSION

The most common causes of rehospitalization of term infants were hyperbilirubinemia and early neonatal infection. Further evaluation of factors associated with readmission and follow-up after discharge may reduce readmission rates. Nutritional errors, which lead to weight loss and infection, can be avoided by following hospital infection prevention rules, such as hand hygiene of mothers and medical staff, and by educating mothers about feeding and the benefits of breastfeeding. Finally, it is necessary to implement quality control measures and carry out regular evaluation of the surveillance program for newborns as the most vulnerable part of the population, in order to assess its effectiveness and identify areas for improvement. We hope that our recommendations can serve as a guide for policymakers, health professionals, and researchers working to address this critical public health issue.

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The Epidemiology of Childhood Epilepsy: A Single Center Survey

Epiledemiologija epilepsije dječije dobi: Studija jednog centra

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ABSTRACT

Introduction: epilepsy is one of the most common neurological diseases that affect more than 50 million people worldwide. In most cases, the disease can be diagnosed by a careful history or observation of attacks. Although the etiological agent can be identified, the cause is still unknown in half of the cases.The incidence rate of epilepsy is 61.4 per 100,000 people. The prevalence of epilepsy varies. In recent decades, the age-specific incidence of epilepsy has decreased over time in the youngest age groups, possibly due to improvements in perinatal care. Aim: The aim of the work is to show the epidemiological characteristics of childhood epilepsy treated at the neuropediatric department of the Sarajevo Pediatric Clinic. Materials and methods: the research is a retrospective, epidemiological study. It included patients diagnosed with epilepsy from January 2021 to December 2024 at the Department of Neuropediatrics of the Pediatric Clinic of the Clinical Center University of Sarajevo. Results: there were 82 (32%) patients aged 1 to 6, 93 (35%) aged 7 to 13, and 58 (22%) aged 14 to 18. Conclusion: in relation to the age of the child, the highest incidence is in the interval from seven to thirteen years of age and the lowest from fourteen to eighteen years of age. According to our research, generalized clonic-tonic seizures, followed by focal ones, were noted in a slightly larger number of subjects. The drug of first choice according to our study is Na valproate and levetiracetam.

Keywords: epilepsy, childhood, incidence, prevalence

SAŽETAK

Uvod: epilepsija je jedna od najčešćih neuroloških bolesti od koje boluje više od 50 miliona ljudi širom svijeta. U većini slučajeva, bolest se može dijagnosticirati pažljivom anamnezom ili posmatranjem napada. Iako se etiološki agens može identificirati, uzrok je još uvijek nepoznat u polovini slučajeva. Stopa incidencije epilepsije je 61,4 na 100.000 ljudi. Prevalencija epilepsije varira. Posljednjih decenija, incidencija epilepsije specifična za dob se vremenom smanjivala u najmlađim starosnim grupama, vjerovatno zbog poboljšanja perinatalne skrbi. Cilj: da se prikažu epidemiološke karasteristike epilpsija dječije dobi liječenih na odjelu neuropedijatrije Pedijatrijske klinike Sarajevo. Materijali i metode: istraživanje je retrospektivna, epidemiološka studija. Uključuje pacijente kojima je epilepsija dijagnosticirana od januara 2021. do decembra 2024. godine na Odjelu za neuropedijatriju Klinike za pedijatriju Sarajevo. Rezultati: u dobi od 1 do 6 godina bilo je 82 (32%) bolesnika, od 7 do 13 godina 93 (35%), a od 14 do 18 godina 58 (22%). Zaključak: prema našem istraživanju, generalizirani kloničko-tonični napadi, a zatim fokalni, zabilježeni su kod nešto većeg broja ispitanika. Lijek prvog izbora prema našoj studiji je Na valproat i levetiracetam.

Ključne riječi: epilepsija, djetinjstvo, incidencija, prevalencija

INTRODUCTION

Epilepsy is one of the most common neurological diseases that affects more than 50 million people worldwide (1). According to the definition, the diagnosis of epilepsy is made if two unprovoked seizures occur apart from 24 hours, or one unprovoked seizure and a 60% risk of another or a diagnosis of epileptic syndrome.

The differential diagnosis of epilepsy includes a number of clinical conditions characterized by transient changes in consciousness and/or behavior. In most cases, the disease can be diagnosed by a careful history or observation of attacks.Although the etiological agent can be identified, the cause is still unknown in half of the cases (2).

The variable genetic predisposition to the occurrence of attacks and the different distribution of some environmental risk factors may explain the heterogeneity of the frequency, course and consequences of the disease in the world. In addition to repeated attacks, there are neurological, cognitive, psychological and social consequences that significantly affect the quality of life of affected individuals and make the disease complex.

People with epilepsy can have seizures, but not all seizures are epilepsy. An epileptic seizure can occur after an acute CNS disease, insult, structural, systemic, toxic or metabolic disorders.

According to the International League Against Epilepsy (ILAE), epilepsy is defined in the following conditions: (1) at least 2 unprovoked seizures occurring >24 h apart; (2) one unprovoked attack and the probability of another attack (at least 60%) as well as after 2 unprovoked attacks, which may occur in the next 10 years; and (3) diagnosis of epileptic syndrome.

An epileptic seizure is a clinical manifestation of abnormal and excessive activity of cortical neurons (3). There can be acute symptomatic attacks, convenient attacks with elevated body temperature and unprovoked attacks. Measures of epilepsy incidence include incidence, prevalence, and mortality. The median frequency of acute symptomatic attacks is 29-39 per 100,000 per year. Occasional attacks predominate in the youngest age group (under 1 year of age) and in the elderly.

The incidence rate of epilepsy is 61.4 per 100,000 people. The prevalence of epilepsy varies significantly between countries depending on the local distribution of risk and etiological factors, the number of seizures at diagnosis and whether only active epilepsy (active prevalence) or including cases in remission (lifetime prevalence) is considered. Approximately 0.9 million children in Europe have active epilepsy, with a prevalence of 4.5 to 5.0 per 1,000. The highest prevalence occurs in children aged 5 to 9 years, at approximately 374.8 per 100,000 (4).

In children, the frequency of epilepsy is highest in the first year of life and decreases to the level of adults by the end of the 10th year of life.

In recent decades, the age-specific incidence of epilepsy has decreased over time in the youngest age groups, possibly due to improvements in perinatal care. In contrast, the incidence increased in the elderly, probably due to increased life expectancy. Focal seizures are the predominant seizure type in children and adults (3).

Prognosis of epilepsy

Epilepsy is a curable condition, with up to 80% of patients having prolonged periods of seizure remission and up to 50% being seizure-free after stopping therapy. Confirmed seizure etiology and specific electroencephalogram (EEG) are the 2 most consistent predictors of recurrence. Epilepsy etiology is the strongest prognostic predictor for seizure recurrence. Epilepsy itself carries a low risk of mortality, but significant differences in mortality rates are expected when comparing incidence and prevalence studies, children and adults, and people with idiopathic and symptomatic seizures. EEG is used to verify the nature of epilepsy in the existing seizures, and more importantly, probably to confirm the precise presence of epilepsy syndrome in patients with drug-refractory epilepsy.

According to the studies on the mental symptoms of children and young people experiencing epileptic seizures, epilepsy patients have a very high risk of mental disorder including depression and anxiety (5).

AIM

The aim of the work was to show the epidemiological characte ristics of childhood epilepsy treated at the neuropediatrics department of the Sarajevo Pediatric Clinic and to determine the prevalence of epilepsy types, age differences, type of therapy and other characteristics by analyzing the collected data.

MATERIALS AND METHODS

Study design

The research is a retrospective, epidemiological study. It includes patients who were diagnosed with epilepsy from January 2021 to December 2024 at the Department of child neurology of the Sarajevo Pediatric Clinic.

Inclusion criteria

Patients were under the age of 18 who were diagnosed with epilepsy after diagnostic processing in the counseling center and the child neurology department.

Exclusion criteria

Patients diagnosed with epilepsy before 2021 and prescribed with additional therapy during the specified period.

Methods

Inpatients included in the research. Gender, age, place of residence, month and year of diagnosis, comorbidities, type of attack, degree of change in electroencephalogram, type of therapy, and changes in MRI of the brain were analyzed.

Statistical analysis

The collected data were analyzed using descriptive statistical methods with the Microsoft Excel program. The data are presented in tables and descriptive. Qualitative variables are shown as absolute numbers and percentages.

RESULTS

A total of 263 patients between the ages of 0 and 18 were included in the study. Out of the total number of patients included in the study, 143 (54%) were male, 120 (46%) were female.

Of the total sample, 30 patients (11%) were aged 0 to 12 months at the time of diagnosis of epilepsy. There were 82 (32%) patients aged 1 to 6, 93 (35%) aged 7 to 13, and 58 (22%) aged 14 to 18.

In 2021, epilepsy was diagnosed in 53 children, in 2022 in 72, in 2023 in 77 and in 2024 in 59 children. In the course of one year, the highest number of newly discovered epilepsies in children is in the period from January to March and in December of the current year, followed by the months of April, May, September, October and November, and the least in the summer period.

Generalized clonic tonic seizures were noted in 190 (72%) subjects, 54 (20%) focal, and 19 (8%) focal with secondary generalization.

In 98 children, the antiepileptic drug of first choice is Na valproate, in 143 children levetiracetam. Other used antiepileptics are vigabatrin, ethosuximide, oxcarbamazepine. The electroencephalogram findings were specifically changed in 210 subjects, non-specifically changed in 3 subjects, normal in 14 subjects and borderline in 36 subjects. In 179 (74%) subjects, the electroencephalogram was slightly altered, in 37 (15%) it was moderately altered, and in 27 (11%) it was severely altered. Magnetic resonance findings were pathological in 120 (45%) subjects, and normal in 143 (55%) subjects.

Table 1 **The most common comorbidities**.

Comorbidity	Number	Percentage (%)
Autism spectrum disorder	29	11
Chromosome pathologies, malformations of the brain	19	7
Condition after ICV	6	2
Cerebral palsy	4	1
State after infection	16	6
other	11	4

In relation to the age of the child, the highest incidence is in the interval from seven to thirteen years of age and the lowest from fourteen to eighteen years of age. According to our research, generalized clonic-tonic seizures, followed by focal ones, were noted in a slightly larger number of subjects. The drug of first choice according to our study is Na valproate and levetiracetam.

DISCUSSION

According to our research, the incidence of epilepsy according to gender is slightly higher in males. In relation to the age of the child, the highest incidence is in the interval from seven to thirteen years of age and the lowest from fourteen to eighteen years of age. According to Begha E, et al., (2020) (2), the frequency is higher in males and in children between the ages of one and ten, which partly coincides with our research. The frequency of childhood epilepsies is similar by age. The frequency is higher in children due to the more extensive diagnostic workup. When the diagnosis of epilepsy is made, only a small number of children can immediately determine the type of epilepsy. That is why the classification is done according to the type of attack. According to our research, generalized clonic-tonic seizures, followed by focal ones, were noted in a slightly larger number of subjects. According to Camfield P, et al., (6) the incidence of focal seizures is somewhat higher compared to generalized clonic tonic seizures. The drug of first choice according to our study is Na valproate and levetiracetam. According to Liang CY, et al. (7), the three most commonly prescribed antiepileptics are Na valproate, levetiracetam and phenytoin, and in patients under 18 years of age also oxcarbazepine. In our study, the electroencephalogram was specifically altered in the majority of subjects. According to Benbadis SR, et al., (8) the routine electroencephalogram has an extremely important value in diagnosing epilepsy, but not the only one. Anamnesis and detailed history still play a major role in this. The electroencephalogram after provocation methods and the one during sleep are also of great importance. The gold standard is prologen video EEG monitoring. According to our research, 55% of the total number of the test subjects has normal brain MRI findings.

According to Ali A, et al., (9), 44% of the subjects had a normal MRI of the brain. The most common comorbidities are disorders from the autistic spectrum. The most common causative factors are malformations of the brain and conditions like infections of the central nervous system. According to Srinivas HV, et al., (10) the most common comorbidity are psychiatric disorders. Epilepsy is more common in autistic individuals than in the general population. The prevalence of epilepsy in autistic individuals in the clinical sample-based studies was higher than that in the population-based based cross-sectional or cohort studies (11).

CONCLUSION

We can conclude that 263 children were diagnosed with epilepsy in a period of four years at the Pediatric Clinic. The number of male children was slightly higher, and the majority was between the ages of 1 and 13. More generalized clonic tonic convulsive seizures with a specific electroencephalographic record were noted. The first line of therapy was Na valproate and levetiracetam.

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Correlation of Anthropometric Measurements of Lower Limbs with Age and Gender within Gymnasium High School Population: Cross-Sectional Study

Korelacija antropometrijskih mjera sa dobom i spolom u okviru gimnazijalske srednjoskolske populacije: presjecna studija.

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ABSTRACT

Introduction: anthropometric measurements play an important role in monitoring the development of the human skeleton and in estimating differences between age or sex group Aim: to compare anthropometric parameters within the secondary school population in relation to the sex and age of the subjects. Material and methods: the study was designed as a cross-sectional descriptive-comparative study that was conducted in the Gymnasium in Zenica. The cross-sectional study included 80 subjects of both sexes, 40 males and 40 females, aged 15 to 19 years (grades I - IV). Results: there was no significant difference in the values of lower limb length from the first to the fourth grade in either male or female sex, but it did between the sexes ($p<0.001$). The length of the lower leg did not have statistically significant differences in values between male sex ($p = 0.431$) and female sex ($p = 0.060$) observed throughout the high school period. Significantly higher values of lower leg length and foot length were found in males ($p<0.001$), but there was no significant difference in the circumference of the upper leg and lower leg between the sexes ($p>0.05$). The results of our work have shown that there is a significant linear relationship between body height and lower limb length, foot length, as well as a significant correlation between male sex and body height ($r=0.614$, $p<0.05$). Conclusion: significantly higher values of antoprometric measurements are present in the male sex. There is a significant linear association of the height and length of the lower limb, as well as the height and length of the foot. Significant correlation between anthropometric measurements and gender is found in most cases in the male sex.

Keywords: anthropological measurements, high school students, lower extremities, age, gender

SAŽETAK

Uvod: antropometrijska mjerenja imaju važnu ulogu u praćenju razvoja ljudskog kostura i u procjeni razlika između starosnih ili spolnih grupa. Cilj: uporediti antropomotrijske parametre u okviru srednjoškolske populacije u odnosu na spol i dob ispitanika Materijali i metode: istraživanje je dizajnirano kao presječna deskriptivno-komparativna studija koja je provedana u Gimnaziji u Zenici. Presječnom studijom je obuhvaćeno 80 ispitanika oba spola, 40 muškog i 40 ženskog spola, životne dobi od 15 do 19 godine (I - IV razred). Rezultati: nije utvrđena značajna razlika u vrijednostima dužine donjeg ekstremiteta od prvog do četvrtog razreda ni kod muškog ni kod ženskog spola, ali jeste između spolova ($p<0,001$). Dužina podkoljenice nije imala statistički značajne razlike u vrijednostima kod muškog spola ($p=0,431$) i ženskog spola ($p=0,060$) promatrano kroz srednjoškolski period. Značajno veće vrijednosti dužine podkoljenice, dužine stopala su pronađene kod muškog spola ($p<0,001$), ali nema značajne razlike u obimu nadkoljenice i podkoljenice između spolova ($p>0,05$). Rezultati našeg rada su pokazali da postoji značajna linarna povezanost tjelesne visine sa dužinom donjeg ekstremiteta, dužinom stopala, kao i značajna povezanost muškog spola i tjelesne visine ($r=0,614$, $p<0,05$). Zaključak: značajno veće vrijednosti antoprometrijskih mjerenja su prisutne kod muškog spola. Postoji značajna linarna povezanost visine i dužine donjeg ekstremiteta, kao i visine i dužine stopala. Značajna povezanost antropometrijskih mjerenja i spola je pronađena u većini slučajeva kod muškog spola.

Ključne riječi: antropološka mjerenja, srednjoškolci, donji esktremiteti, dob, spol

INTRODUCTION

Anthropometric measurements have important role in monitoring the development of the human skeleton and in estimating differences between age or gender groups (1,2).

Throughout history, several studies in this field have been published. In a study conducted in Iran among students aged 18-25, Moshkdanian and colleagues observed a correlation between the length of the lower limbs and the feet with growth. The results showed that the length of the lower extremities was a more significant indicator of growth compared to the length of the foot (3,4). Through his study, Ahmed et al. concluded that the length of the lower limbs of the Sudanese population depends on gender. (5) Previous studies have shown that it is possible to determine the height of a person based on the length of the ulna (6).

Anthropometric measurements are an important part of medical science, especially for human anatomy and forensic medicine, and that puberty or high school is the period when these values approach those of adulthood, it is necessary to examine anthropometric indicators within the high school population.

AIM

The aim of the study was to show anthropometric parameters of high school students in first, second, third and fourth grade and to compare between grades and gender and examine the association of anthropometric parameters with gender, age and height.

MATERIALS AND METHODS

Materials and study design

The study was designed as a prospective, cross-sectional descriptive-comparative study that was conducted at the Gymnasium Secondary School in Zenica. Permission was previously obtained from the school management and the consent of the parents/guardians of the children, who gave / did not give their consent through informed consent.

Methods

The cross-sectional study included 80 subjects of both sexes; 40 males and 40 females aged 15 to 19 years. Subjects included in the study were subjected to measurement of anthropometric parameters in physical health education classes, in the sports hall of the Gymnasium Secondary School Zenica, from first to ninth November 2024. The data were collected by measuring anthropometric parameters using following anthropometric instruments: lever scale (Figure 1), centimetre tape (Figure 2), and anthropometer (Figure 3).

Subjects were classified into four groups according to the class they attended:

1. Group of subjects attending the first grade (n=20)
2. Group of subjects attending the second grade (n=20)
3. Group of subjects attending the third grade (n=20)
4. Group of subjects attending the fourth grade (n=20)

Subjects were classified into two groups according to gender within the class:

1. Group of male subjects (n=10)
2. Group of female subjects (n=10)

The criteria for inclusion in the study were: subjects (students) whose parents/guardians have given their consent to participate by signing an informed consent and subjects (students) who were present at physical education classes during the research period
The criteria for exclusion from the study were: subjects (students) whose parents/guardians have not given their consent to participate by signing an informed consent and subjects (students) who were not present at physical education classes during the research period. Each participant had the following anthropometric measurements taken total body weight and height, length of lower limb, length of lower leg, length of the foot, circumference of the upper leg and circumference of the lower leg. The measurements were taken using lever scale, anthropometer and centimetres tape.

Within our sample, we made the following measurements:
- Body weight was measured on a lever scale, which should be calibrated regularly. When measuring, the subject was without clothes and shoes or only in underwear. The clothes that the subject keept on should later be weighed separately and the resulting mass should be deducted from the first measure.
- Body height (length) - standing height must be measured in the following conditions: a person stands with a full foot on a hard surface, without shoes and socks, keeps the heels together and stretched completely, shoulders relaxed. Height is measured with an anthropometer or stadiometer, with the examiner usually standing behind the subject's back. The horizontal arm is lowered until it touches the scalp (vertex)

The length of the lower limb is measured with an anthropometer. The subject takes the same position as when measuring body height. The skeletal process of the spina iliac anterior superior is determined by the third finger of the hand, which simultaneously holds the horizontal arm of the anthropometer. This part of the instrument is then pressed against the spin and then the apparent distance from the floor.

Figure1 **Lever scale**

Figure 2 **Centimetre tape**

Figure 3 **Anthropometer**

- The length of the lower leg was measured with a vertically placed anthropometer while the subject was standing. This was the distance between the points of the malleolar and the tibial.

- The length of the foot was measured with an anthropometer. The subject would take a sitting position, placing the left foot on the horizontal arm of the anthropometer by touching the transverse arm with his heel. The second arm of the anthropometer was brought to the tip of the longest toe.

- The circumference of the upper leg was measured with a centimetre tape. The subject should stand slightly apart so that the weight of the body was evenly distributed on both legs.A centimetre strip was placed under the gluteal sulcus.

- The circumference of the lower leg was measured with a centimetre strip that was placed in a horizontal position, at its maximum size. The subject would sit on the table, and his legs were free.

Statistical Analysis

The results were elaborated and documented in detail and presented in absolute numbers, relative numbers, statistical values with the use of statistical indicators, and presented in simple and comprehensible tables and graphs.

The results of descriptive statistical analysis were presented with the following parameters: mean value ± standard deviation or median with interquartile range. Categorical variables were presented by frequency as an absolute number or in percentages. Differences between groups were tested by ANOVA test for dependent samples. The Shapiro-Wilk test was used to test the significance of the difference in deviation from the normal distribution. The connection between predictors was tested by Pearson's correlation test, and the influence of several predictors was tested by multiple regression. The results were presented tabularly or graphically, and the accepted statistical level of significance of the difference is $p<0.05$. SPSS computer program version 24.0 was used for statistical analysis.

RESULTS

The study involved 80 subjects, 40 males and 40 females. Demographics are shown in Table 1.

Table 1 **Demographic characteristics.**

Variables	**Male**	**Female**	**Total**	
n	*40*	*40*	*80*	
%	*50*	*50*	*100*	
age	*16.75+1.01*	*16.78+1.02*	*16.86+1.01*	*p=0.871*

The age distribution is represented by the mean value and standard deviation.

The average length of the lower limb is shown in Figure 1.There was no significant difference in the length of the lower limb from the first to the fourth grade of male subjects (p=0.235), as well as female (p=0.834). Statistically significantly higher values of lower limb length in men were found (p<0.001). (Figure 1)

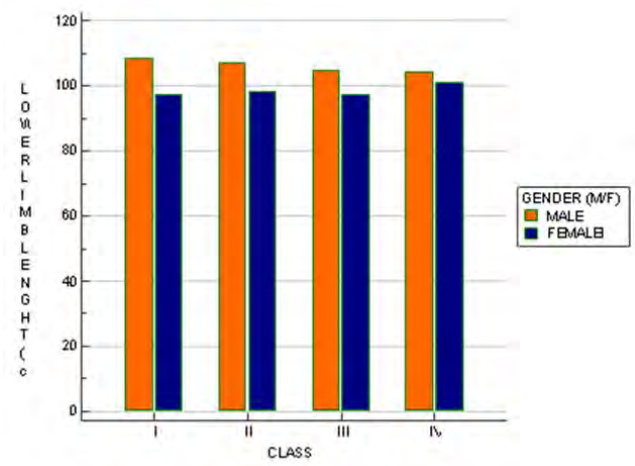

Figure 1 **Average length of the lower limb.**

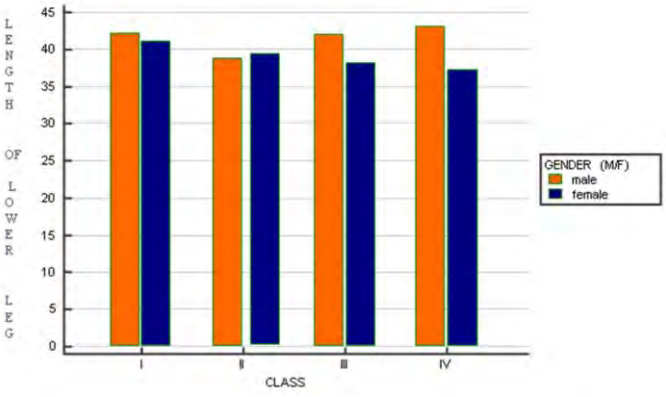

Figure 2 **Average length of the lower leg.**

There was no significant difference in foot length from the first to the fourth grade in male subjects (p=0.672), as well as female (p=0.208). Statistically significantly higher values of foot length in men were found (p<0.001). (Figure 3)

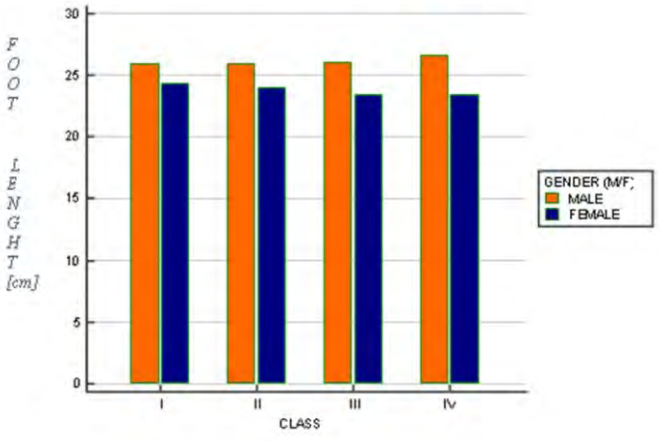

Figure 3 **Average foot length.**

There was no significant difference in the circumference of the upper leg from the first to the fourth grade of male subjects (p=0.300), as well as in the female sex (p=0.843). No statistically significant differences in the circumference of the upper leg between the sexes (p=0.661) were found (Figure 4).

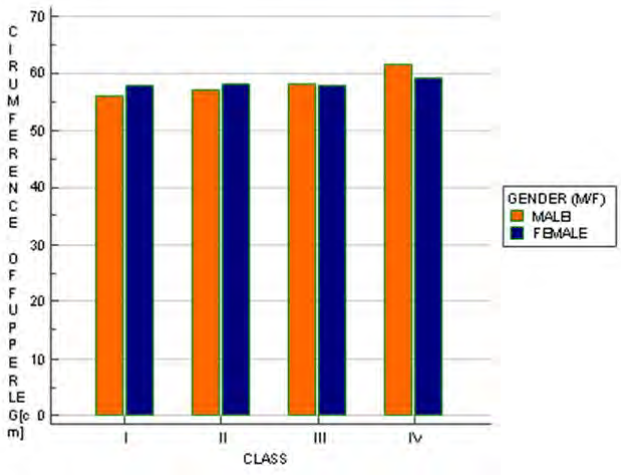

Figure 4 **Average circumference of the upper leg.**

Also, results didn't show difference significant difference in the circumference of the lower leg from the first to the fourth grade of male subjects (p=0.420), as well as within the female sex (p=0.493) and between the sexes (p=0.644). (Figure 5)

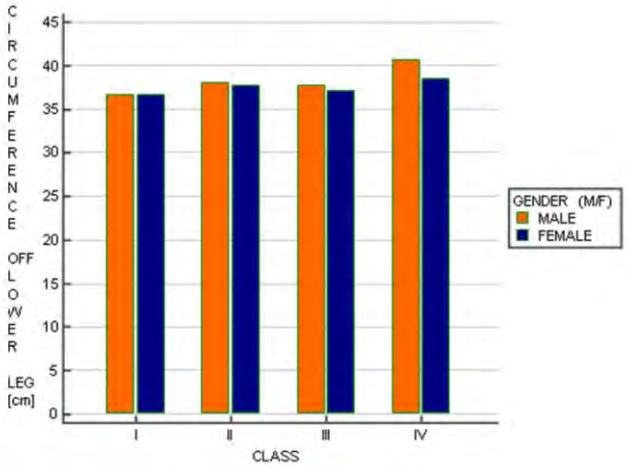

Figure 5 **Average circumference of the lower leg.**

Regression analysis determined the value of the regression factor R = 0.932, with the effect between the height and length of the lower limb (p<0.001); Height and length of the foot (p<0.001) (Table 2).

Table 2 **Regression analysis compared to height with other anthropometric measurements.**

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics			
					R Square Change	F Change	df1	df2
1	0.932	0.87	0.82	3.61	0.87	16.89	20.00	51.00

	Model	Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4396.316	20	219.816	16.893	.000
	Residual	663.634	51	13.012		

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	41.167	16.345		2.519	0.015	8.353	73.981
	BODY WEIGHT (kg)	0.001	0.109	.002	.010	0.992	-.218	.221
	LENGTH OF LOWER LIMB (cm)	0.398	0.118	.326	3.374	0.001	.161	.635
	LENGTH OF LOWER LEG (cm)	-0.120	0.239	-.055	-504	0.616	-.600	.359
	LENGTH OF FOOT (cm)	1.908	0.535	.392	3.565	0.001	.833	2.982
	CIRCUMFERENCE OF UPPER LEG (cm)	0.153	0.171	.096	.897	0.374	-.189	.496
	CIRCUMFERENCE OF LOWER LEG (cm)	0.033	0.096	.022	.344	0.732	-.160	.226

Correlation of anthropometric measurements with age and gender showed a significant association of gender and body weight in the second, third and fourth grades ($p<0.05$), correlation between sex and body height in all four classes ($p<0.05$), as well as in limb length ($p<0.05$). A significant correlation was observed between gender and lower leg length in the third and fourth grades ($p<0.05$), as well as foot length in the first, third and fourth grades ($p<0.05$) (Table 3).

Table 3 **Correlation of anthropometric measurements with age and gender.**

VARIABLES		I class		II class		III class		IV class	
		AGE	GENDER (M/F)	AGE	GENDER (M/F)	AGE	GENDER (M/F)	AGE	GENDER (M/F)
AGE	r	1	-0.101	1	0.2	1	0.14	1	-0.229
	p		0.673		0.398		0.556		0.331
BODY WEIGHT (kg)	r	-0.011	-0.408	-0.045	-.608*	-0.354	-.593**	0.037	-.449*
	p	0.964	0.074	0.85	0.004	0.125	0.006	0.878	0.047
BODY HEIGHT (cm)	r	0.122	-.515*	-0.09	-.614**	-0.127	-.659**	.467*	-.754**
	p	0.609	0.02	0.707	0.004	0.593	0.002	0.038	0.001
LENGHT OF LOWER LIMB (cm)	r	-0.03	-.763**	-0.428	-.591**	0.007	-.653**	0.37	-.469*
	p	0.901	0.001	0.077	0.01	0.975	0.002	0.119	0.043
LENGHT OF LOWER LEG (cm)	r	0.393	-0.328	0.338	-0.2	0.023	-.520*	0.363	-.775**
	p	0.086	0.158	0.145	0.398	0.924	0.019	0.116	0.002
FOOT LENGHT (cm)	r	0.068	-.471*	0.302	-0.436	0.02	-.623**	0.356	-.692**
	p	0.776	0.036	0.195	0.055	0.932	0.003	0.124	0.001
CIRCUMFERENCE OF UPPER LEG (cm)	r	-0.16	0.221	-0.113	0.116	-0.272	-0.115	-0.276	-0.041
	p	0.501	0.348	0.634	0.625	0.246	0.629	0.24	0.864
CIRCUMFERENCE OF LOWER LEG (cm)	r	-0.044	0.068	-0.217	-0.202	-.504*	-0.062	-0.087	-0.139
	p	0.853	0.777	0.357	0.392	0.023	0.796	0.717	0.558
	p	0.952	0.001	0.303	0.001	0.628	0.009	0.949	0.004
VARIABLES		I class		II class		III class		IV class	
		AGE	GENDER (M/F)	AGE	GENDER (M/F)	AGE	GENDER (M/F)	AGE	GENDER (M/F)
GENDER (M/F)	r	-0.101	1	0.2	1	0.14	1	-0.229	1
	p	0.673		0.398		0.556		0.331	

DISCUSSION

The study included 80 subjects of secondary school age (grades I-IV), of which 40 subjects were male with an average age of 16.75±1.01 years, and 40 female subjects with an average age of 16.78±1.02 years.

Our study didn't show a difference in body height from the first to the fourth grade of male subjects (p=0.666), as well as female (p=0.966). Statistically significantly higher values of body height in the male sex were found (p<0.001). The study included 500 students (M = 250; F = 250) aged 18-23 years sexual dimorphism and correlations between anthropometric indicators of feet and body height. The results showed that the values of foot length and body height were higher in men than in women (P<0.01). The length of the foot is also the best indicator for determining body height. Based on the results, they concluded that there is geographic and sexual dimorphism in anthropometry, which is significant in criminology and forensics (7). Results did not show difference in the length of the lower limb was found from the first to the fourth grade of male subjects (p=0.235), as well as female (p=0.834). However, higher values of lower limb length in men were found (p<0.001). According to literature, anthropometric measurements showed that there is a statistically significant difference in the length of the lower extremities between the sexes, as well as that the male sex has longer lower extremities (P < 0.05) (8). Previous studies have shown that the length of the lower leg is greater in the male sex than in the female sex (P<0.001) (5). We did not reveal a significant difference in foot length from the first to the fourth grade in male subjects (p=0.672), as well as female (p=0.208) and higher values were found for the length of the foot in the male sex (p<0.001). In his study, which included 103 subjects aged 21 to 23, Jakhar, JK, et al., compared the length of the feet between the sexes. The results of the study showed that the male sex has longer feet than the female (P<0.001). (9) Our results did not show a significant difference in the circumference of the lower leg from the first to the fourth grade of male subjects (p=0.420), nor within the female sex (p=0.493) and significant differences in lower leg circumference between the sexes (p=0.644). Woyn M, et al. conducted a study engaged in ballet. They measured individual anthropometric parameters, among which is the circumference of the lower leg. The results showed that the circumference of the lower leg was statistically significantly larger in the male sex compared to the female sex (10). The difference can be explained by the fact that the children in the second grade in our study were extensively involved in sports, especially the female sex of the subjects. Processing the results of the measurement did not reveal a significant difference in the circumference of the upper leg from the first to the fourth grade of male subjects (p=0.300), as well as in the female sex (p=0.843). No statistically significant differences in the circumference of the upper leg between the sexes (p=0.661) were found. We have not found any recent references available for this parameter. The regression analysis determined the value of the regression factor R=0.932, with an impact in 87% of cases. A significant influence between height and length of the lower extremity was found (p<0.001); height and length of the foot (p<0.001). Grivas TB, et al. in their work, which included 5093 subjects, showed that there was a statistically significant association between body height and body weight in the subjects. The regression factor was determined: R=0.852. The results of the study also showed that there was no statistically significant difference between the sexes for the measured anthropometric parameters (11). The study involved 359 medical students in Kerala showed a statistically significant correlation between body height and lower limb length, but in different percentages. The length of the tibia showed the highest percentage correlation with body height (12). A similar study was carried out by Arora M. The results of the study showed a statistically significant correlation between body height and lower limb length, as well as foot length (13).

In a similar study Gupta P, et al. examined the association between tibial length and body height. The results of the study showed that there is a statistically significant correlation between body height and tibia length (14). In their work, Agarwal S, et al. examined the correlation of body height with foot length and lower leg length (15).

As part of our research, by examining the correlation of anthropometric measurements with age and gender, we indicated that there is a significant correlation between gender and body weight in the second, third and fourth grades (p<0.05). There is a significant correlation between sex and body height in all four classes (p<0.05), as well as in limb length (p<0.05). A significant correlation was observed between gender and lower leg length in the third and fourth grades (p<0.05), as well as foot length in the first, third and fourth grades (p<0.05).

The limitations of this study include the small sample size and one region of country. Future studies with larger sample size could help in overcoming this limitation.

CONCLUSION

We believe that the results of this study open the perspective for further research related to bioanthropological indicators, affirmed within the framework of precise population indicators and sexual dimorphism. We founded relationship between body height with lower limb length, and foot length. Also there was a relationship between male sex with body height and lower limb length. Higher values of body height and body weight were determined in the male sex.

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Predictive Value of Intratumoral Expression of CD 34 and CD105 in the Occurrence of Metastases in Intrathoracic Lymph Nodes in NSCLC

Prediktivna vrijednost intratumorske ekspresije CD 34 i CD105 u pojavi metastaza u intratorakalnim limfnim čvorovima kod NSCLC

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ABSTRACT

Introduction: lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 2.48 million new cases and 1.8 million deaths globally, respectively. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases, with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma being the most frequent, with several other types that occur less often, but all types can occur in unusual histological variants. Aim: to determine the expression of CD34 and CD105 molecules on the cancer blood vessels and their association with the lymph node involvement, primarily in correlation with the N1 and N2 lymph node status in NSCLC. Materials and methods: the study included 120 patients with NSCLC, who underwent one of the anatomic resection procedures on the lungs with lymphadenectomy or biopsy of lymph nodes with histopathological examination of specimens according to the current TNM classification, where the strength of tumor markers CD34 and CD105 was determined and lymph node status evaluated. Result: almost half of the patients in this study did not have metastases of the primary NSCLC in the intrathoracic lymph nodes (N0). In 38.3% of the patients, N1 lymph node metastases were found, whereas 15% had N2 lymph node metastases. Conclusion: AFCD105 is a good predictor of NSCLC metastasis to intrathoracic lymph nodes, both N1 and N2. In comparison to CD33, the CD105 cancer marker proved to be a better predictor of lymph node involvement.

Keywords: Non-Small Cell Lung Cancer, CD34 Antigen, CD 105 Antigen, TNM Staging

SAŽETAK

Uvod: karcinom pluća je vodeći uzrok smrti povezanih sa malignim neoplazmama u svijetu, sa približno 2,48 miliona novih slučajeva, odnosno 1,8 miliona smrtnih slučajeva širom svijeta. Nemikrocelularni karcinom pluća (NSCLC) čini 85% svih slučajeva karcinoma pluća, pri čemu su adenokarcinom, skvamocelularni i karcinom velikih stanica najčešći, uz nekoliko drugih tipova koji se rjeđe javljaju, ali svi se tipovi mogu pojaviti u neobičnim histološkim varijantama. Cilj: utvrditi ekspresiju molekula CD34 i CD105 na krvnim žilama karcinoma i njihovu povezanost sa zahvaćenošću limfnih čvorova, prvenstveno u korelaciji sa statusom limfnih čvorova N1 i N2 u NSCLC. Materijali i metode: istraživanjem je obuhvaćeno 120 bolesnika s NSCLC-om, kod kojih je učinjen jedan od anatomskih resekcionih zahvata na plućima uz limfadenektomiju ili biopsiju limfnih čvorova, uz histopatološku pretragu preparata prema važećoj TNM klasifikaciji, gdje je određena ekspresija CD34 i CD105 te evaluiran status limfnih čvorova. Rezultat: gotovo polovina bolesnika u ovoj studiji nije imala metastaze primarnog NSCLC u intratorakalnim limfnim čvorovima (N0). U 38,3% bolesnika nađene su metastaze u limfnom čvoru koji odgovara N1 statusu, dok je 15% imalo metastaze u limfnom čvoru N2 statusa. Zaključak: AFCD105 je dobar prediktor NSCLC metastaza u intratorakalne limfne čvorove, i N1 i N2. U komparaciji sa CD33, marker CD105 pokazao se boljim prediktorom zahvaćenosti limfnih čvorova.

Ključne riječi: nemikrocelularni karcinom pluća, CD 34 antigen, CD105 antigen, TNM klasifikacija

INTRODUCTION

Lung cancer is gender-wise the second most common cancer (prostate cancer in men and breast cancer in women are only more prevalent) and by far the leading cause of cancer deaths worldwide (1). It represents 11% of all new cancer cases in men and 12% of all new cancer cases in women. Generally, there are two main types of lung cancer: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). A third less common type of lung cancer could be considered carcinoid. NSCLC makes up about 80% of all lung cancer cases (2).

The therapy of NSCLC is multimodal with mandatory consideration of surgical treatment in the form of either non-anatomical (wedge) or anatomical resection, such as segmentectomy, lobectomy, bilobectomy, or pulmectomy with radical lymphadenectomy. Intrathoracic nodal involvement (according to the TNM classification and evaluated through the 'N' status) as a common pathway for lung cancer metastasis, is considered one of the most reliable prognostic indicators in these patients (3).

Tumor angiogenesis, expressed as the intratumoral microvessel density (IMVD) and determined and quantified using specific antibodies against endothelial cells (EC), is closely related to tumor growth, metastasis to intrathoracic lymph nodes, and postoperative prognosis in patients with NSCLC (4,5). Commonly used anti-EC antibodies bind to the cell surface protein CD34, which acts as an adhesion factor, and CD105, which can bind transforming growth factor β1 and transforming growth factor β3. Antibodies to CD105 have been shown to have a greater affinity for "activated" and "newly generated" ECs in tissues that participate in angiogenesis. Unlike pan-EC antibodies such as CD34, antibodies to CD105 can preferentially react with ECs of all angiogenic tissues, including tumors, but weakly or not at all with those of most normal tissues, which may suggest the superiority of CD105 as a marker of angiogenesis in clinical studies.

Decisive definition of all pathological features of malignant tumors that are considered high-risk factors for metastases or recurrence of the underlying malignant disease in patients with NSCLC who underwent resection can help stratify patients postoperatively into precisely defined groups with different degrees of risk, which would enable a better setting for decision making on postoperative, i.e. adjuvant treatment.

AIM

The aim of this study was to determine the correlation of CD34 and CD105 expression on the cancer blood vessels and their association with the lymph node involvement as a significant prognostic factor in NSCLC.

MATERIALS AND METHODS

This retrospective study conducted at the Clinic of Thoracic Surgery, Clinical Center University of Sarajevo, (tissue sampling) and the Department for Pathological-Anatomical and Molecular Diagnostics of the Joint Medical Service of the Institute for Pulmonary Diseases of Vojvodina - Sremska Kamenica (histopathological and immunological staining and testing), included 120 consecutive adult subjects with NSCLC, who underwent anatomic lung resection with lymph node biopsy or lymphadenectomy during one-year period, i.e. between 1 June 2016 and 1 June 2017.

Each subject was given an accurate histopathological diagnosis according to the current eight TNM classification system (UICC and AJCC in 2016). In all 120 subjects, additional histopathological staining with antibodies/markers for CD34 and CD105 was performed, which enabled the determination of the intensity of their expression along with the determination of the microvascular density of blood vessels MVDCD34 and MVDCD105 and the surface fraction of both mentioned markers AFCD34 and AFCD105.

The surface fraction (AF) of blood vessels positive for CD34 and CD105 markers was also analyzed. With the help of an add-on called Analyze Particles, the surface fraction was determined for both markers (AFCD34, AFCD105).

Descriptive statistical methods used measures of central tendency (Arithmetic mean), measures of variability (Standard deviation), and relative numbers (Structure indicators). X^2 test, Fisher's exact test, Mann-Whitney U test, and Kruskal-Wallis test as non-parametric statistical analysis methods were also used. Binary and multinominal logistic regression analysis was performed to analyze the predictive ability of morphometric parameters. Fisher's exact test and X^2 test were considered statistically significant when p values wereXless than 0.05.

RESULTS

This study included 120 patients, among them 78, i.e. 65% male, and 42, i.e. 35% female patients. The average age was 62.53. The subjects were divided into four age groups (55-59, 60-64, 65-69, and 70-74 years - the youngest patient was 55 and the oldest was 74 years old).

Adenocarcinoma was found in 53.3% (64 patients), whereas squamous cell carcinoma was histopathologically verified in the remaining 46.7% (56) patients. We did not verify other types of NSCLC among patients in our study.

Lobectomy was the modality of choice in 82 patients, i.e. 68.3% of all cases. Pneumonectomy was performed in 26 patients (21.7%) and bilobectomy in the remaining 12 patients (10%). In 46.7% of cases no cancer cells were indicating a metastasis of primary NSCLC to intrathoracic lymph nodes (N0). Metastases in lymph nodes (N1 status) were found in 38.3% of patients, whereas a positive N2 status was observed in 15% of cases. N3 lymph node involvement was not confirmed in our sample.

Vascular invasion was found in 27.3%, i.e. in 30 patients. Analyzing the relationship between the two different types of NSCLC found in this study (adenocarcinoma and squamous cell carcinoma), no correlation was found between the type of tumor and the presence of vascular invasion (Fisher's test=0.02; p = 0.99).

Using the Kruskal-Wallis analysis, it was found that when it comes to the intrathoracic lymph node metastatic spread of cancer cells, MVD and AF for the CD34 marker do not differ from each other at different stages of spread. However, it was observed that for the CD105 marker, there is a reduced surface fraction at the N2 stage compared to the N0 and N1 stages. The MVD of blood vessels at different stages of extension to intrathoracic lymph nodes does not statistically significantly differ.

When analyzing the MVDCD34 and AF CD34 for with the occurrence of metastases in intrathoracic lymph nodes, no significant difference was found in regard to the involvement of different stages of lymph nodes (N descriptor of the TNM classification). However, it was observed that for the CD105 marker, there is a statistically significant difference in the AFCD105 in lymph node metastases of N2 cells compared to N0 and N1 cells. The MVDCD105 also does not have a statistically significant difference at different levels of involvement of intrathoracic lymph nodes (Table 1).

Table 1 **Kruskal-Wallis analysis of the association between microvascular density of blood vessels and surface fractionfor markers CD34 and CD105 with the occurrence of metastases in intrathoracic lymph nodes - "N" descriptor (n = 120).**

	N0	N1	N2	χ^2	p
MVD_{CD34}	23.20	27.30	29.80	1.25	0.54
AF_{CD34} (%)	2.96	3.07	3.08	0.07	0.96
MVD_{CD105}	16.30	15.80	17.60	1.98	0.37
AF_{CD105} (%)	1.73	1.75	1.50	8.39	0.02*
* statistically significant					

In total, 34 (28.3%) patients with NSCLC had moderate expression intensity, while 86 subjects (71.7%) had a strong expression intensity of the CD34 marker (Table 2).

Table 2 **Frequency of expression intensity for the CD34 marker.**

Expression intensity	Frequency	Percentage (%
0 (none)	0	0
1 (weak)	0	0
2 (moderate)	34	28.3
3 (strong)	86	71.7

On the other hand, 26 (21.7%) patients had weak, 60 (50%) had moderate, while 34 (28.3%) patients had a strong expression intensity of the CD105 marker (Table 3).

Table 3 **Frequency of expression intensity for the CD105 marker.**

Expression intensit	Frequency	Percentage (%)
0 (none)	0	0
1 (weak)	26	21.7
2 (moderate)	60	50.0
3 (strong)	34	28.3

Using the Mann-Whitney test, a significant statistical difference was observed between the number of blood vessels and the surface fraction for the CD34 marker. Patients with adenocarcinoma have higher values of MVD and AF than patients with squamous cell carcinoma (Table 4). When it comes to MVD and AF for the CD105 marker, no significant statistical differences were observed between patients with different cancer types.

Table 4 **Mann-Whitney analysis of microvascular blood vessel density and surface fraction for markers Cd34 and CD105 in different types of NSCLC (n = 120).**

	Adenocarcinoma	Squamous cell carcinoma	U / z	p
MVD_{CD34}	29.95	23.35	1090/-3.69	< 0.001*
AF_{CD34} (%)	3.26	2.72	1316/-2.50	0.012*
MVD_{CD105}	16.75	15.70	1632/-0.84	0.40
AF_{CD105} (%)	1.53	1.66	1692/-0.53	0.59
* statistically significant				

Based on the multinomial logistic regression, it was determined that AFCD105 is a good predictor of the lymph node metastatic spread of cancer cells (Table 5).

Table 5 **Microvascular blood vessel density and surface fraction for markers CD34 and CD105 as predictors for evaluating the lymph node metastatic spread of cancer cells.**

Morphometric parameters	N stage			
	N1 stage OR (95% CI)	p	N2 stage OR (95% CI)	p
MVD_{CD34}	1.05 (0.98-1.12)	0.12	1.03 (0.95-1.21)	0.49
AF_{CD34} (%)	1.06 (0.71-1.59)	0.76	1.18 (0.70-1.97)	0.54
MVD_{CD105}	0.96 (0.87-1.05)	0.37	1.01 (0.89-1.15)	0.85
AF_{CD105} (%)	0.63 (0.40-0.99)	0.046*	0.47 (0.22-1.02)	0.049*
Reference category: N0 stage				

DISCUSSION

This retrospective study included 120 patients who, due to a verified NSCLC, underwent anatomic lung resection with lymphadenectomy or lymph node biopsy. Histopathological examination of resected specimens was performed. Every patient obtained a definitive diagnosis according to the TNM classification system (8th revision of the TNM classification published by UICC and AJCC in 2016). All surgical procedures were performed at the Clinic for Thoracic Surgery, Clinical Center University of Sarajevo. In contrast, all specimens were analyzed at the Joint Medical Services of the Institute for Pulmonary Diseases of Vojvodina - Sremska Kamenica during one year, i.e. between 1 June 2016 and 1 June 2017.

In all 120 subjects, additional histopathological staining of specimens with antibodies/markers for CD34 and CD105 was performed, which allowed determination of the intensity of their expression along with determination of MVD, i.e. MVDCD34 and MVDCD105 and the surface fraction of both mentioned markers, i.e. AFCD34 and AFCD105.

Out of the total of 120 patients included in this study, 78 of them (65%) were male, while 42 (35%) were female. The average age of the patients included in our study was 62.53 years. The youngest patient was 55 and the oldest was 74 years old. Adenocarcinoma was found in 53.3% (64) of patients, and squamous cell carcinoma in the remaining 46.7% (56). We did not verify other types of NSCLC. Regarding the type of surgical resection, lobectomy was most often performed - in 82 (68.8%) patients. Pulmectomy was performed in 26 (21.7%) and bilobectomy in 12 (10%) patients.

Analyzing the data, the majority of patients included in the study (46.7%) did not have metastases of primary NSCLC to intrathoracic lymph nodes (N0). In 38.3% of patients, metastases were found in N1 lymph nodes and in 15% of subjects in N2. No metastases were confirmed in N3 lymph nodes. Considering the correlation of two types of NSCLC - adenocarcinoma and squamous cell carcinoma with the occurrence of metastases within intrathoracic lymph nodes, a statistically significant difference was found between these two types of cancer (X^2=11.08; p=0.004). In the study by Luo T, et al., metastases in N1 lymph nodes was found in 1.73% of patients with adenocarcinoma and in 20.00% of patients with squamous cell carcinoma, whereas in our results as many as 23.7% of patients with adenocarcinoma and 15.3% of patients with squamous cell carcinoma had N1 lymph node metastases (6). On the other hand, metastases in N2 lymph nodes were found in 9.83% of patients with adenocarcinoma, and in 8.00% of patients with squamous cell carcinoma, respectively. However, the majority of patients (88.44% with adenocarcinoma and 72.0% with squamous cell carcinoma) did not have metastases in intrathoracic lymph nodes. In our study, 11.9% of patients with adenocarcinoma and 3.4% with squamous cell carcinoma had N2 lymph node metastases.

Our study found a relatively high percentage of patients who did not have metastases in the intrathoracic lymph nodes - 28.8% with squamous cell carcinoma and 16.9% with adenocarcinoma, which is in agreement with the aforementioned study but also with most other authors, only our percentage of patients without metastases is far lower than in the literature, which can be explained to some extent by better preoperative staging and better early diagnosis of NSCLC. We believe that the high percentage of N0 and N1 stages in various studies may be a consequence of the described non-specificity of clinical rather than pathological staging, i.e. publication of results that are not based on histopathological verification of the presence or absence of metastases in the intrathoracic lymph nodes (7,8).

Out of 120 of our subjects included in this study, vascular invasion was found in 30 (27.3%) patients. Analyzing the relationship between the two different types of NSCLC found in this study (adenocarcinoma and squamous cell carcinoma), no correlation was found between the type of tumor and the presence of vascular invasion (Fisher's test=0.02; p = 0.99). Most authors agree that the level of tumor angiogenesis has proven to be a good prognostic predictor for most cancers and thus for NSCLC, and the majority of authors conclude that increased tumor vascularization indicates a tendency for better survival of tumor cells and a worse prognosis of disease outcome and better resistance of cancer to therapy (9,10).

Our results showed that all patients had an expression of both biomarkers but with different intensities. Strong expression of the CD34 marker was found in 86 (71.7%) and moderate in 34 (28.3%) patients. Observing the expression of the CD105 biomarker, 26 (21.7%) patients had a weak, 60 (50%) patients a moderate, and 34 (28.3%) remaining patients had a strong expression of this biomarker. In comparison with the study by Miyata Y, et al., the expression of this biomarker was higher, as well as the absolute values of MVDCD34, which were higher compared to MVDCD34 and/or MVDCD105, which is in accordance with our results (11).

Moreover, we found that MVDCD34 is almost double in value in comparison to MVDCD105 as well as the AFCD34 and AFCD105. These results are in accordance with contemporary literature data that compared MVD or AF determined by CD34 and CD105, and the majority of authors explain such a difference also found in our results by the fact that CD34 as a hematopoietic progenitor cell antigen stains the endothelial cells of neoplasia stronger than normal endothelium, and constitutes a very sensitive marker of endothelial differentiation, however, the anti-CD34 antibody also stains fibroblasts, adipocytes, and lymphatic endothelial cells, which is considered the explanation in these studies but also our results with higher expression of CD34 and higher absolute values of MVDCD34 in comparison with the expression of CD105 and MVDCD105.

Kumar P, et al., have shown that CD105 antibodies preferentially react with activated endothelial cells (EC) in tissues involved in neoangiogenesis such as tumor tissues, and that antibodies against pan-EC cells such as CD34 antibodies react with both normal vessels and activated blood vessels of neovascularization (12). When analyzing the MVDCD34 and AFCD34 and the occurrence of metastases in intrathoracic lymph nodes, no significant difference was found in relation to the involvement of different stages/levels of lymph nodes. However, it was observed that for the CD105 marker, there is a statistically significant difference in the value of the surface fraction in lymph nodes affected by N2 lymph node metastases to N0 and N1 stage.

Based on the results of multinominal logistic regression, the AFCD105 is a good predictor of metastases in intrathoracic lymph nodes. In our study, patients who had a higher value of AFCD105 were found to be 37% more likely to not have NSCLC metastases in N1 lymph nodes, compared to patients with a verified N0 stage. This suggests that a lower value of AFCD105 will predict a higher likelihood of NSCLC metastases in N1 lymph nodes, i.e. AFCD105 is 37% lower in patients with metastases in N1 compared to patients with N0. Moreover, patients with higher AFCD105 values had a 53% lower probability of metastases in N2 lymph nodes compared to the group of patients with N0 stage, which means that lower values of AFCD105 predict occurrence and metastases in N2 lymph nodes. Nevertheless, multinominal logistic regression did not show good predictive properties of morphometric parameters for MVDCD34 and MVDCD105, or the AFCD34 for the occurrence of NSCLC metastases in intrathoracic lymph nodes.

A study by Tanaka F, et al., argues that evaluated neoangiogenesis in NSCLC by comparing anti-CD34 and anti-CD105 antibodies showed a greater specificity and thus the superiority of CD105 as a marker of angiogenesis in NSCLC (13). The authors explained that the morphometric parameters of neovascularization of MVDCD105 were more closely correlated with VEGF expression than MVDCD34. Such studies have been conducted on various types of cancer, but no satisfactory number of data and works have been found that deal with the quantification of neovascularization determined by CD34 and CD105 in NSCLC and the correlation with metastasis to intrathoracic lymph nodes, which is recognized as one of the basic factors for the outcome of treatment of patients with NSCLC.

CONCLUSION

There is no significant difference in the correlation of MVDCD34, AFCD34, and MVDCD105 with the occurrence of NSCLC metastases in different localizations of intrathoracic lymph nodes. However, there is a statistically significant difference in the value of AFCD105 in lymph nodes affected by metastases in N2 compared to N0 and N1 lymph nodes. A lower value of AFCD105 predicts a higher probability of NSCLC metastases in the N1 lymph nodes. A lower AFCD105 value represents a good predictor of metastasis to N2 lymph nodes in patients with NSCLC. CD105 marker proved to be a better predictor of lymph node metastasis in comparison to the CD34.

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Cystic Fibrosis - Experience in Treatment with a New Modular Therapy at the Pediatric Clinic of the Clinical Center University of Sarajevo

Cistična fibroza - iskustva sa liječenjem uz novu modularnu terapiju na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu

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ABSTRACT

Cystic fibrosis is the most common hereditary disease caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The impaired electrolyte homeostasis caused by the mutated or missing protein leads to symptoms in various organ systems. However, the pulmonary manifestation with chronic infections and eventually respiratory failure remains the most important threat. Until a decade ago, only symptomatic treatment was available. However, since 2012, different combinations of CFTR modulators have been available for people with cystic fibrosis (pwCF) carrying different mutations. The advent of these drugs has impressively changed the life expectancy and quality of life of people with cystic fibrosis and raised new challenges in terms of long-term complications and the phasing out of conventional therapies. In Bosnia and Herzegovina, treatment with CFTR protein modulators and their combinations is available from December 2023 for children with manifest cystic fibrosis who carry the deltaF 508 mutation heterozygous or monozygous and are over 6 years old. Aim: this review provides an update on the latest developments in the diagnosis, treatment and prognosis of children with cystic fibrosis (pw CF) and their application in the Pediatric Clinic in Sarajevo. Conclusion: the introduction of CFTR modulators into the treatment of patients with cystic fibrosis is an important step forward. Nevertheless, there is the need for continuous and controlled therapy and further centralised monitoring of the patient.

Keywords: cystic fibrosis, CFTR modulators

SAŽETAK

Cistična fibroza (CF) je najčešća od svih rijetkih bolesti, značajno skraćuje životni vijek, a uzrokovana je defektom u genu za transmembranski regulator provodljivosti jona (CFTR-eng. cystic fibrosis transmembrane regulator). Kod pacijenata sa cističnom fibrozom poremećena je homeostaza elektrolita , što se očituje simptomima u više organskih sistema. Plućne manifestacije - bronhiektazije praćene hroničnim infekcijama a na kraju respiratornom insuficijencijom ostaju i dalje najvažnija prijetnja životnom vijeku bolesnika. Do prije deset godina bilo je dostupno samo simptomatsko liječenje, a od 2012. godine, pojavom tzv. modulatora CFTR-proteina, perspektiva i kvaliteta života osoba s cističnom fibrozom značajno se promijenila. Sa novim lijekovima postavljeni su i novi izazovi u vezi sa dugoročnim komplikacijama zbog eventualnog smanjenja konvencionalne terapije, ali i sa finansiranjem liječenja koje je mnogim pacijentima još uvijek nedostupno. U Bosni i Hercegovini (BiH) od decembra 2023.godine dostupno je liječenje modulatorima CFTR-proteina injihovim kombinacijama za djecu sa manifestnom cističnom fibrozom koje nose mutaciju deltaF 508 heterozigot ili monozigot uzrasta iznad 6 godina. Cilj rada: analizirati bazične i nove spoznaje u dijagnostici, liječenju i prognozi pedijatrijskih pacijenata oboljelih od cistične fibroze te prikazati primjenu na Pedijatrijskoj klinici u Sarajevu. Zaključak: uvođenje CFTR modulatora u liječenje bolesnika s cističnom fibrozom važan je korak naprijed. Ipak, postoji potreba za kontinuiranom i kontroliranom terapijom te daljnjim centraliziranim praćenjem bolesnika.

Ključne riječi: cistična fibroza, CFTR modulatori

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease caused by a mutation of the gene located on the long arm of chromosome 7, that is responsible for protein synthesis, the so-called cystic fibrosis transmembrane regulator (CFTR). To avoid the negative connotation of the term "mutation", it is now recommended to use the name "variant", which is also used in this sense in the text (1).

The gene was identified 30 years ago and since then over 2000 variants of CFTR have been discovered. The most common variant is delta F508del (Phe508del; c.1521_1523delCTT), in which phenylalanine is replaced at position 508 on chromosome 7. Worldwide, about 80–90% of people with CF have at least one copy of the F508del CFTR variant, although the prevalence of this variant varies from population to population (2). Among the people receiving treatment in Croatia, 81.1% are carriers of the F508del variant, making Croatia one of the countries with the highest incidence of this variant after Denmark (83.2%) and Albania (81.2%). These are the data from the European Cystic Fibrosis Society Patient Registry (ECFSPR) for 2021, which includes 54,043 patients from 40 countries. By 2019, 31 patients were registered in our country. Of all registered individuals, 80% are carriers of this variant, and half of them are homozygous for F508del, while 20% of patients have another combination of CFTR gene variants (3). CF is a multisystemic disease with the highest prevalence in the white ethnic groups, i.e. in Europe, North America and Australia. There are approximately 90,000 people with CF worldwide. The disease is characterised by chronic infections and inflammation of the respiratory tract, pancreatic insufficiency and malnutrition, diabetes, liver disease, obstruction of the vas deferens with consequent infertility in almost all men and premature death. There is a wide range of disease severity with a median survival age that is now around 50 years (4). Since the first description of the disease by Dorothy Andersen in 1938 (5), many findings related to CF have appeared to date - understanding the nature of the disease, diagnostics, different types of treatment, the organisation of treatment and monitoring of patients, the discovery of the CFTR gene, the use of "new" drugs and a personalised approach to the treatment of patients (2,4).

Our research has provided brief insights that allow a better understanding of the treatment of patients with CFTR modulators, a therapy that has greatly changed the lives and prospects of most CF patients. In addition to a brief overview of the theoretical facts, the basic indicators of the results of the treatment of our patients are presented, which, in addition to the mentioned therapy, is the result of the commitment of many health care workers and related professions who, despite numerous obstacles, persistently and devotedly follow modern trends and thus contribute to improving the quality of life of patients with CF in B&H.

CFTR protein synthesis and pathophysiology

The synthesis of the CFTR protein is a complex process that begins with the transcription of CFTR DNA (deoxyribonucleic acid), which takes place in the cell nucleus with the formation of messenger ribonucleic acid (mRNA), which binds to ribosomes in the cell cytosol after passing through the nuclear membrane. The mRNA decoding process, known as translation, and the synthesis of a polypeptide chain of 1480 amino acids based on the standard genetic code of CFTR take place on the ribosomes. Further biosynthesis of the CFTR protein continues with post-translational modifications and conformational folding of the protein through the endoplasmic reticulum (ER) and the Golgi body (GT) until the final formation of the mature form of the protein. In the entire process of the formation of a functional protein, certain steps within the biosynthesis of the CFTR protein are still partially unknown. The process of CFTR protein formation is ineffective and slow even in the so-called "normal" situation, in the wild variant of the gene, so that in healthy humans only a small part, 20-30% of the newly synthesised CFTR protein is finally formed into a functional mature CFTR protein. Its amount in the cell membrane then varies depending on the balance between the anterograde pathway through the cell, endocytosis and its recycling, i.e. degradation (6, 7). The CFTR protein functions as a chloride and bicarbonate channel. Loss of functional CFTR protein leads to reduced release of chloride from the epithelial cells, which subsequently leads to desiccation of the secretion on the surface of the epithelial cells and a change in the pH and osmolarity of the secretion. CFTR also regulates the activity of other important processes within the cell, including the activity of other ion channels, such as the epithelial sodium channel (ENaC). Disruption of CFTR function therefore leads to a decrease in the reabsorption of sodium and water via ENaC, which further contributes to the dehydration of the superficial fluid layer of the cell and the ineffectiveness of mucociliary activity. Furthermore, CFTR dysfunction also affects mitochondrial function and innate immunity mechanisms, leading to deregulation of inflammatory processes. All these disturbances create an environment in the airways that is prone to uncontrolled inflammatory processes and chronic bacterial infections, particularly with Pseudomonas aeruginosa (6-8). Although several processes inside and outside the cell are affected by the dysfunctional CFTR protein, it is generally assumed that the disruption of chloride transport is the main pathophysiological driver of the disease. At the same time, the change in the function of the chloride channel is an easily accessible marker for all processes that play a role in CF, whereby chloride test in sweat is relatively easy to perform and of great diagnostic importance, as well as for monitoring the efficacy of new drugs (9). To date, more than 2,000 variants of the CFTR protein are known, but the significance of many variants is unknown. Most CFTR variants are rare and have no confirmed association with the disease, however, their large number indicates a lack of stability of the CFTR gene (2). An international project is currently underway - the CFTR 2 database, which links basic clinical data to the genotype of people with CF and is updated regularly. According to the latest published data, 719 variants causing CF and 49 variants with variable clinical significance have been recorded (10).

Classification of CFTR variants

There are numerous classifications of CFTR variants that help to understand the consequences of the molecular defect. The most widely accepted classification comprises six different classes. The consequences of different pathogenic variants of the CFTR protein can manifest themselves in the absence of functional protein synthesis (class I), in disorders in the formation, "folding", of proteins and their degradation during passage through the cell cytoplasm (class II), inefficient opening of the CFTR channels (class III), disruption of the conductivity and anion selectivity of the CFTR channel (class IV), reduced synthesis of functional protein (class V) and reduced protein stability in the cell membrane, i.e. its faster degradation (class VI) (8). Each class is associated with a different severity of disease, depending on the degree of CFTR dysfunction and thus the clinical and prognostic implications for patients. Severe manifestations of the disease are in classes I-III, milder ones in classes IV-VI. In heterozygotes for two different classes of CFTR mutations, the clinical picture is usually milder, although it should be noted that the final expression of CF also depends on other factors, such as modifying genes, environment, therapeutic approaches, etc. In addition, some variants may have features of more than one class. For example, the most common variant F508del, which is classified as class II, has features of both class III and class VI (8,11-14). There is a classification system with a seventh class that includes CFTR variants in which no mRNA is present (12). The most frequently cited classification with six classes, in which the class I variants (without functional CFTR protein) are divided into two subclasses, one of which has no mRNA necessary for the translation process (class I a) and the other the synthesis of a non-functional protein (class I b) (13,14).

Treatment for Cystic fibrosis

Cystic fibrosis affects several organ systems, which makes the treatment of this disease very complex. Therefore, patients with CF should be treated in a specialised centre where treatment is provided by a multidisciplinary team consisting of physicians, "CF specialists", who can be recruited from different specialties (primarily pulmonologists, gastroenterologists, but increasingly also endocrinologists, ENT specialists , geneticists, clinical pharmacologists and, more recently, gynaecologists and oncologists), nurses ("CF nurses" trained in the treatment of patients with CF), physiotherapists, dieticians, psychologists and social workers (15,16). Such a structured multidisciplinary treatment approach, in line with European and global standards, has been favoured worldwide for many years. There are 281 in the USA, 39 in England, 63 in Spain, etc. and in neighbouring Croatia (as of 2017) the so- called Centre for Cystic Fibrosis in Children and Adults (17).

The treatment regimen has changed drastically since the disease was first described, from the era before antibiotics, until today (5,18). Until ten years ago, traditional treatment of patients with CF had focussed on symptomatic treatment of the affected organ systems, especially the pulmonary and gastrointestinal consequences of the disease. The use of chest physical therapy to improve secretion clearance in the respiratory tract with inhaled mucolytics, secretolytics and antibiotics (systemic, inhaled) as well as pancreatic enzymes and vitamins to control malabsorption has led to a significant prolongation of life expectancy and a change in patient structure (almost half, in some cases more, are adults) and improvement in the quality of life of patients in recent decades. However, despite the progress made in extending median life expectancy (>40 years), the daily implementation of the extensive and complex therapy, which requires more than 4 hours of daily commitment, is a major burden for each patient in real life and affects adherence to therapy (18).The identification of the CFTR gene more than 30 years ago (1989) (19, 20) focussed research on trying to resolve the underlying genetic defect, i.e. on treatment strategies that could correct the underlying genetic defect. The potential benefits of such a therapy would be large and should theoretically be suitable for the treatment of all individuals with CF, regardless of genotype variant. Various approaches to gene therapy have been investigated, ranging from attempting to deliver a normal CF gene or mRNA into the respiratory tract via viral or non-viral vectors, to the use of technologies that enable so-called gene editing, i.e. CFTR DNA or mRNA, e.g. such as CRISPER-Cas9 (eng. clustered regulatory interspaced short palidromc repeats) and other techniques, but to date none of these approaches have proven to be a viable treatment option (14, 18, 21). Therefore, research is focussed on finding other therapeutic approaches. Thanks to effective methods for screening potential therapeutic molecules in cell models, which can be tested in vitro (e.g. (e.g. nasal epithelial cells, pluripotent haematopoietic stem cells and intestinal/respiratory models, so-called organoids) to predict the clinical response to the drug (14, 22-25)), small molecules that can improve the function of the abnormal CFTR protein have been identified, i.e. the so-called CFTR modulators (18, 26). With the discovery of CFTR modulators and their application, there has been a major shift in the treatment and real life of patients with CF, from treating the symptoms and consequences of the disease to treating the pathophysiological cause of the disease - the existing CFTR protein defect. The possible application of such a therapy at an early stage of life opened up the prospect of indescribable changes in the lives of patients, from the manifestation of the disease to the prevention of a whole range of complications, but also new questions.

CFTR modulators

CFTR modulators are small molecules taken orally and «modulate" the function of the abnormal CFTR protein in the body. In contrast to gene therapy, they do not change the CFTR gene, but "manipulate" it; they intervene in the process of creating the end product of the genetic CF variants. To date, several possible modes of action of CFTR modulators are known. One possibility is the stabilisation of the CFTR protein, the so-called stabilisers, with the result that the activity time of the CFTR protein is extended. The so-called enhancers would increase the amount of mRNA and thus CFTR protein formed immediately after the translation process, would allow other modulators to act on a larger amount of the protein thus formed. Molecules that would make it possible to interrupt protein synthesis during the translation process at the ribosomes are stop codon readers (14, 15, 25). In addition to the potential modulators of the effects described above, there are already two other types of modulators in clinical practise today: CFTR potentiators and CFTR correctors. Potentiators, i.e. enhancers potentiate the cAMP-mediated activity of the CFTR channel, while correctors correct defects in the formation of the CFTR protein during passage through the cell cytoplasm (at the level of the ER, GT, etc.) (6, 14, 18). In practical application, four molecules are available, i.e. four therapeutic molecules are registered: one CFTR potentiator and three correctors and their combinations (1, 14, 18). The first small molecule to become clinically available for people with CF was ivacaftor (Kalydeco®). It is a potentiator that enhances chloride transport across the apical membrane of the cell by prolonging the time the CFTR channel is open. It was originally approved in the USA in 2012 for the G551D mutation (Gly551AspCFTR; class III mutation) (27-29). Today, ivacaftor is approved in the US for children one month of age and older who have one of the 97 mutations susceptible to the potentiator's action. In Canada and the EU, it is approved for children four months of age and older, and it is available in another dozen countries where it is approved for different age groups and number of mutations. Randomised clinical trials have shown that ivacaftor has a positive

effect on lung function, weight gain and quality of life in different age groups. The mean increase in the percentage of predicted forced expiratory volume in 1 s (FEV1% p.v.) was about 10% in the first short-term follow-up studies. Further studies have shown that ivacaftor is effective when not only the short-term effects on FEV1% p.v. and/or body mass index are observed. The most impressive result was a 55% reduction in pulmonary exacerbations in the population with the G551D variant, with long-term data after 5.5 years of therapy showing an effect on multiple outcome levels including lung function. There is also evidence that treatment with ivacaftor positively affects both insulin secretion in individuals with impaired glucose tolerance and hepatic steatosis in individuals with CF-related liver disease (14, 32). Ivacaftor has been shown to has a good tolerability and a safe profile, despite being registered up to three times in 30 of patients, especially in the younger ones. The results obtained from the use of ivacaftor were significant for the entire CF community in that they confirmed a new therapeutic approach by showing that it is possible to repair the function of the mutated CFTR protein and thus act on the manifestations of the disease, including those that were considered irreversible. Today, Iva Caftor in combination with two other modulators - Elexacaftor/Tezacaftor/IvaCaftor (E/T/I) - is an essential component of the triple therapy approved in the USA in 2019 for the treatment of patients with CF. The first corrector to show an effect on the F508del variant in experiments and then enter the clinic was lumacaftor (32). Its use as a monotherapy was disappointing, with no significant effect on lung function (33,34), only in combination with ivcaftor did it show some improvement in patients with the most common variant of CFTR (35). The first dual combination of corrector and potentiator, lumacaftor/ivacaftor (L/I), Orikambi®, was approved in 2015, and in 2018 another tezacaftor/ivacaftor (T/I) combination, called Symdeko® in the US and Symkevi® in the EU, was also approved (14,30,36). Both are combinations of a corrective agents (lumacaftor or tezacaftor) and a potentiator (ivacaftor). Lumacafor and Tezacaftor stabilise the CFTR protein during its formation by passing through the cell, and subsequently the function of the CFTR channel improves under the action of the potentiator. The clinical effect of the L/I combination showed a modest but still significant effect on improving lung function in F508del homozygotes (increase in FEV1% b.v. by 2.6 – 4%), but the effect in heterozygotes with an F508del variant was insignificant. Although the mode of action is the same for the T/I and L/I combination, the T/I combination showed a slightly better effect on lung function (increase in FEV1% p.v. by 4% in homozygotes, i.e. 6.8% in heterozygotes) with a decrease in pulmonary exacerbations, fewer side effects and a better interaction profile with other drugs (14, 18, 26, 35, 36). While the L/I combination is only approved for F508del homozygotes over the age of 2 years, the T/I combination is approved for patients over the age of 6 years with two F508del variants or with one F508del variant and one of 150 additional variants with residual function. The next-generation corrector, elexacaftor, which also targets the most common F508del variant, differs from lumacaftor and tezaxaftor in that it targets the formation of the CFTR protein in a new, different way and at a different site. Elexacaftor not only acts as a corrector, but has also been shown to have potentiator properties (14, 38). The first triple combination with this modifier was approved in the USA at the end of 2019: Elexacaftor/Tezakaftor/Ivacaftor (E/T/I) under the name (Trikafta®) for patients over 12 years of age. The indication was later expanded so that it was approved for use in children aged 6 years and older in mid-2021 and for even younger children aged 2 years and older from 2023. Initially, the drug was approved for F508del homozygotes and F508del heterozygotes in combination with a number of variants that responded to the drug in in vitro studies, so that from 2023 it will be approved for all patients with at least one F508del variant, regardless of the other pathological variant. In practise, this means that around 80% of all people with CF have a genotype that is suitable for therapy with this drug. In 2021, a triple combination, E/T/I, was approved in the EU under the name Kaftrio® for patients over the age of 12, and at the end of 2022 for patients aged 6 and over (39). Studies have confirmed the higher efficacy of the triple modulator combination (E/T/I) compared to the previously approved single or dual modulator combinations. The efficacy is reflected in improved lung function (increase in FEV1% p.v. from 10 to >14%) (33), a better pulmonary clearance index, fewer pulmonary exacerbations and a decrease in the chloride concentration in sweat (by approx. 41.5 mmol/L). An improvement in body mass index and quality of life was also observed in the patients. The role in cystic fibrosis-related diabetes (CFRD) is not yet clear. The drug has been shown to have a favourable safety profile with mild to moderate side effects. The most common side effects are cough, upper respiratory tract infections such as colds, flu (influenza), increased sputum production, sinus inflammation and nasal congestion or nasal discharge. Headache, increase in blood pressure, stomach and abdominal pain, diarrhoea, skin rash, increase in liver enzymes (three times the normal level for their age in 10.6 % of patients), creatine phosphokinase and bilirubin in the blood and, rarely, damage to the lens of the eye have been described. in childhood (clouding of the lens that does not affect vision) (14,37). In an attempt to predict the effects of triple modulation therapy (E/T/I), a group of authors from Canada (37) developed a microsimulation model and used it to analyse data from the Canadian patient registry. The model is based on quantifying the potential impact of CFTR modulator triple therapy and analysing differences in treatment outcomes in different treatment scenarios, from baseline CF treatment without modulator therapy to outcomes after early or late introduction of CFTR modulator therapy. The distribution of disease severity, need for transplantation, frequency of exacerbations and median survival age were simulated. Despite some limitations and shortcomings (including pharmaceutical industry support), this simulation analysis showed that the introduction of triple modulation therapy reduced the number of milder and the number of more severe forms of the disease and the need for transplantation compared to patients without modulator therapy. The frequency of exacerbations is also lower after the introduction of triple therapy compared to the dynamics of exacerbations in patients without modulators. The authors also compared the effects of CFTR modulators depending on the age at which treatment was started. It was shown that a "later" introduction of the therapy, i.e. two years later compared to an "early" introduction, also has a positive effect on the course of the disease, but with a later onset and a slightly weaker effect on the reduction of pulmonary exacerbations. Positive effects were also observed with the "later" introduction: a lower incidence of more severe forms of the disease, a lower need for transplantation and an prolongation of the median survival age, but all of the above effects were less pronounced than with the early introduction of the therapy. Unfortunately, not all CF patients benefit from the effective CFTR modulators currently available, either because their CFTR variant is rare or the therapy is simply not available to them (1). Currently, several pharmaceutical companies are investigating new potential CFTR modulators that are in various stages of preclinical and clinical testing, giving hope for further improvements in the efficacy and safety of the therapy. There is also a European project called Human Individualised Treatment for CF (HIT-CF), which is ongoing in 16 different countries and aims to obtain modulators for patients with particularly rare mutations (1, 11,25). Finally, it should be noted that therapy with CFTR modulators today is also associated with significant financial costs, which limits the availability of treatment for all patients who fulfil the medical requirements, so that there is considerable inequality in access to these drugs worldwide. It is likely that more and more modulators will come onto the market in the future. The CF community will therefore also need to find ways to make these drugs more accessible to patients, especially those with rare variants of the CFTR gene.

Application of CFTR modulators in Pediatric Clinic of the Clinical Center University of Sarajevo

In the Federation of Bosnia and Herzegovina, treatment with CFTR modulators was approved with certain restrictions by the Institute for Health Insurance (ZZO) in November 2023, despite many obstacles. The triple combination E/T/I (Kaftrio®+Kalydeco® tablets) is approved for patients over 6 years of age who are homozygous for the F508del variant or with an F508del and a minimal function long variant. In December 2023, treatment with CFTR modulators was started for children and adults in the Federation of Bosnia and Herzegovina who fulfil the diagnostic criteria. In the Federation of Bosnia and Herzegovina, our clinic has received a list of patients with cystic fibrosis, including 10 paediatric patients (6-18 years old), one of whom has changed his place of residence and is no longer insured with us. Seven patients are under 6 years old, one patient with other gene mutations or variants and two children are receiving CF therapy and have no confirmed mutation based on the clinical picture. Candidates for modular therapy are not patients after lung transplantation, children under 6 years of age and those with unfavourable genetics. Therefore, from the initial total number (31/2019. European Registry) in our clinic, 9 paediatric patients met the criteria for the use of approved CFTR modulators, of course with the hope that the number will increase somewhat due to the expansion of indications, the adolescence of some of the young patients (<6 years) and/or with newly diagnosed paediatric patients. The implementation of the therapy in the Federation of Bosnia and Herzegovina was agreed at the national level with the Institute for Health Insurance and Reinsurance (ZORFBIH) with central participation and with regular periodic monitoring and control of paediatric and adult patients in clinical centres in Sarajevo, Mostar and Tuzla. Since the approval of CFTR modulator therapy in the Federation on 22 November, 2023 until January 2024, this form of treatment was offered and introduced to all patients who met the criteria. In fact, 29% of paediatric candidates (9/31 children) are successfully treated with CFTR modulators and controlled according to a pre-established protocol adapted to our clinical conditions, that includes all the prescribed procedures. The medication is taken daily in two doses with a high-fat meal (20 g). Patients and their doctors are obliged to report adverse events, clinical and therapeutic changes (e.g. introduction of antibiotics). To make it easier for patients, they are also provided with remote monitoring, including spirometry at home, urine saturation and the like, contact by telephone and e-mail, depending on financial possibilities. Objective parameters are used to assess the effectiveness of the therapy. Respiratory status, i.e. lung function (FEV1% p.v.) for people aged 6 and over, the frequency of pulmonary exacerbations, the number of hospitalisations and the consumption of antibiotics due to pulmonary exacerbations, then nutritional status, i.e. BMI and changes in chloride concentration in sweat, must be monitored and reported regularly to the ZZOiRFBiH. Other laboratory parameters are also monitored - in particular indicators of liver function and pancreatic status (faecal elastase-1) as well as respiratory tract colonisation with characteristic pathogens and initial values of lipid status due to late complications such as arteriosclerosis. In children, ophthalmological examinations and other available objective tests are mandatory. No less important is the subjective assessment of the patient and family, i.e. quality of life and daily functioning. The Lung Clearance Index, which is one of the methods used worldwide to monitor the success of therapy, is not available in our country. Since the end of 2023, 9 patients with cystic fibrosis have been treated and monitored with CFTR modulators in the paediatric clinic, in addition to other symptomatic and supportive therapies. The paediatric patients take Kaftrio® and Kalydeco® twice in the morning and evening with a meal, with the dose depending on body mass and weight respectively. In the meantime, one patient has changed his insurance, i.e. his place of residence, and fulfils two main criteria, namely a typical gene variant and age (>6 years).

We present an analysis of the data of these patients (9) and compare them with unpublished data of the same patients from the year before the application of the modulator when it comes to cultures of the respiratory tract.

Gender distribution: 4 girls (7 years, 8 years, 14 years and 17 years) and 4 boys (13 years, 10 years, 15 years, 11 years, 17 years). The age range extends from 7 to 17 years. All patients with an F508del variant, homozygotes or heterozygotes, who have another mutation in addition to F508del or the other is unknown. The patients generally tolerated the therapy well, more than half had no side effects. One boy developed urticarial rash, there was a seven-day break and the treatment was resumed, now without the occurrence of urticaria. One patient developed a febrile fever in the first few days, which was later no longer recorded.

The most serious side effect was recorded in one boy in the form of repeatedly elevated concentrations of aminotransferases, which no longer occurred after 3 months at the control examination, but hyperglycaemia did. Other side effects observed were mild and transient, without additional therapeutic measures being taken. The most common side effect was increased cough and expectoration in the first days or weeks of therapy, in more than half of the subjects (7/9). In two subjects, the initial cough was followed by wheezing and in one subject a sparse haemoptysis. Headache, dizziness and light-headedness were noted in one subject (4/9), and our patients did not report any change in mood or impulsive behaviour. After increased cough and sputum production in the first days or weeks of therapy, most subjects produce much less secretion and may even fail to produce sputum. Therefore, monitoring the bacteriology of the respiratory tract is difficult, as more than half of the subjects are unable to provide a sputum sample, so a throat swab was analysed instead. Chronic or intermittent bacterial colonisation with Staphylococcus aureus and/or Pseudomonas aeruginosa was present in 51% of cases. Microbiological and molecular analysis of the isolates from the respiratory tract revealed 18 pathological samples before therapy and 19 after the introduction of CFTR modulators. Colonisation with the bacterium Pseudomonas aeruginosa was present in 51% of cases (18, 35) of the respiratory samples before treatment with CFTR modulators, with the use of CFTR modulators the condition is still practically the same. The occurrence of colonisation with the bacterium Stenotrophomonas maltophylia was not observed, nor were other opportunistic infections.

In the observed 4-month interval after the start of therapy, a significant change in nutritional status was observed, as assessed by the z-score for BMI. Before therapy, it was desirable to be well nourished (i.e. BMI z-score >0), and after 4 months of therapy, the proportion of adequately nourished children increased to 7/9, although it should be noted that two children were on the borderline of having a BMI that was too high. Before therapy, the median z-BMI in the study group was -0.73 (range: -2.91 to +1.65), and after 4 months of therapy with CFTR modulators, the median z-BMI was -0.33 (range: -3.99 to 1.96), representing an absolute increase in BMI of 0.32 SD

During the controls, patients often reported a better general condition, endurance and fitness, which can be objectified by a 6-minute walk test and a comparison of the length of the walking distance before and during therapy, which we did not monitor. The chloride concentration in sweat before and during therapy was also analysed. The average chloride concentration in sweat before therapy was 113 mmol/L, and only one subject had intermediate values. After 4 months, all subjects had normal chloride concentrations in their sweat

CONCLUSION

The introduction of CFTR modulators into the treatment of patients with cystic fibrosis is an important step forward, regardless of variations in response to therapy, adverse events and the like. A positive change can be seen in the improvement of lung function, a lower number of lung exacerbations and hospitalisations. The use of antibiotics has also been reduced and in future it will be possible to modify the basic therapy depending on the patient. Apart from the respiratory system, the changes are most evident in the improvement of nutrition, the reduction of symptoms on the digestive system, the improvement of muscle strength and then we expect an impact on comorbidities such as diabetes or hepatic steatosis. Most importantly, the patient's quality of life has fundamentally changed for the better, which is our ultimate goal in the treatment of chronic paediatric patients. The results of monitoring therapy with CFTR modulators at the Pediatric Clinic of the CCUS, although they concern only a relatively small number of patients, show that they are comparable to the results and observations in other countries where they are used. When analysing patient outcomes, it is of particular importance that we have a database of all CF patients, as in other countries, in order to better identify and quantify treatment outcomes and side effects and to compare the condition of patients over time, including the era prior to the use of CFTR modulators. In addition, with such systematic monitoring, potential adverse effects can be more easily observed, which should encourage caution and additional monitoring and ultimately provide insights, good or bad, into a fascinating, under-researched therapeutic area of medicine. We are of course pleased that treatment with CFTR modulators has brought significant changes for the better to patients, but much remains to be evaluated, e.g. how early, i.e. when it is optimal to start therapy and how to assess the condition at the initiation of therapy in patients who do not yet have symptoms of the disease, what the long-term effects of these drugs and side effects are, i.e. whether there is a time limit for the use of this therapy, and how and when the existing basic therapy should be modified by the use of modulators. We should also anticipate the introduction of new drugs and their combinations in the future. The above-mentioned unknowns and circumstances, including the high cost of therapy, are of particular importance not only for patients, but also for physicians and for the health insurance system of each country. All this points to the importance, but also to the need for continuous a*nd controlled therapy and further centralised monitoring of the patient.*

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Zygomaticofacial Foramen: A Morphological Study on Dry Skulls of the Bosnian and Herzegovinian Population

Foramen zygomaticofaciale: morfološka studija na suhim lubanjama Bosansko - Hercegovačke populacije

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ABSTRACT

Introduction: a thorough understanding of the zygomaticofacial foramen (ZFF) is essential for various maxillofacial, implantological, and aesthetic procedures, as its manipulation carries a significant risk of neurovascular injury. Aim: to analyze the ZFF's shape, diameter, and location, as well as its spatial relationships with key anatomical landmarks. Materials and methods: this study examined 57 adult human skulls, applying standard morphometric measurements with sliding calipers. The number, size, shape, and location of the ZFF were recorded bilaterally, and its distances from surrounding landmarks were measured. Statistical analysis was performed using conventional methods. Results: in 114 sides examined, the ZFF was absent in 4.4% of cases. The frequency of foramina per side was: one (40.4%), two (36.8%), three (10.5%), four (5.3%), and five (2.6%). The average vertical and transverse diameters were 0.83 ± 0.31 mm and 0.70 ± 0.29 mm, respectively. The majority of foramina were oval (69%), while 25.5% were round, 4.0% semilunar, and 1.5% irregular. The ZFF's mean distances to surrounding anatomical structures were: 7.22 mm (infraorbital margin), 26.83 mm (frontozygomatic suture), 20.34 mm (zygomaticomaxillary suture), 22.90 mm (zygomaticotemporal suture), and 8.62 mm (most prominent point of the zygomatic bone). Conclusion: the variability in the number and position of the zygomaticofacial foramen (ZFF) should be carefully considered when administering regional block anesthesia or performing surgical and aesthetic procedures in the zygomatic region.

Keywords: zygomatic bone, zygomaticofacial foramen, maxillofacial surgery, craniometry, anatomical variation

SAŽETAK

Uvod: poznavanje zigomatikofacijalnog foramena (ZFF) je od ključne važnosti za različite kirurške, implantološke i estetske zahvate, jer nepažljivo rukovanje ovim područjem može izazvati ozbiljne neurovaskularne povrede. Cilj: proučiti oblik, promjer i položaj ZFF-a, te njegove odnose s drugim anatomskim strukturama. Materijali i metode: ispitano je 57 ljudskih lubanja, a pomoću standardnih morfometrijskih tehnika zabilježeni su obostrano podaci o broju, obliku i poziciji ZFF-a, te su izmjerene njegove udaljenosti od okolnih anatomskih struktura. Rezultati su analizirani standardnim statističkim metodama. Rezultati: među 114 analiziranih strana, odsustvo ZFF zabilježen je u 4,4% slučajeva. Jedan otvor zabilježen je u 40,4%, dva u 36,8% slučajeva, tri u 10,5%, četiri u 5,3% i pet u 2,6% slučajeva. Prosječna vrijednost vertikalnog i transverzalnog dijametra zigomatikofacijalnog otvora iznosila je 0,83 ± 0,31 mm odnosno 0,70 ± 0,29 mm. Najčešće zabilježeni oblik zigomatičnofacijalnog otvora bio je ovalni oblika (69%), a onda slijede okrugli (25,5%), polumjesečasti (4,0%) i na kraju nepravilni (1,5%). Srednje vrijednosti udaljenosti ZFF-a do okolnih anatomskih struktura bile su: 7,22 mm (infraorbitalni rub), 26,83 mm (frontozigomatski šav), 20,34 mm (zigomatikomaksilarni šav), 22,90 mm (zigomatikotemporalni šav) i 8,62 mm (najistaknutija točka zigomatične kosti). Zaključak: različiti oblici i pozicije ZFF-a moraju se uzeti u obzir pri izvođenju kirurških i estetskih zahvata u zigomatičnom području, kako bi se izbjegle komplikacije povezane s neurovaskularnim strukturama.

Ključne riječi: os zygomaticum, foramen zygomaticofacialis, maksilofacijalna hirurgija, kraniometrija, anatomska varijacija.

INTRODUCTION

The zygomatic bone (ZB) is a key structural component of the midface, contributing to its contour and forming portions of the orbital floor and lateral wall. As a crucial element of the viscerocranium, it articulates with multiple skull bones, including the maxilla, sphenoid, frontal, and temporal bones, playing a significant role in facial architecture (1). The zygomatic bone (ZB) functions as a critical link between the middle and upper facial skeleton while also serving as the origin point for the masseter and zygomatic (major and minor) muscles. Structurally, it features three significant openings: the zygomaticofacial (ZFF), zygomaticoorbital (ZOF), and zygomaticotemporal (ZTF), which provide pathways for nerves bearing the same names (2). In some cases, a delicate arterial branch stemming from the infraorbital artery may course through the zygomaticofacial foramen (ZFF) (3,4).

The zygomatic nerve is an essential branch of the maxillary nerve, which itself is the second division of the trigeminal nerve. Upon passing through the zygomaticoorbital foramen (ZOF), it splits into the zygomaticofacial and zygomaticotemporal nerves. Responsible for sensory innervation, the zygomaticofacial nerve conveys stimuli from the skin covering the most prominent area of the face (5). Conversely, the zygomaticotemporal nerve is responsible for conducting sensory stimuli from the skin of the temporal region, specifically above the zygomatic arch (ZA), while functioning similarly to the zygomaticofacial nerve (2).

Although previous morphological research has identified variations in the ZFF's incidence, size, and position, further investigation is necessary to fully grasp their impact on surgical planning. Understanding the anatomical characteristics of the ZFF has numerous clinical applications, particularly in maxillofacial surgery. This knowledge is vital for procedures such as facial trauma reconstruction, correction of deformities, cosmetic enhancements, and dental surgeries involving zygomatic implants (4,5,6,7).

During these procedures, trauma to the branches of the zygomatic nerve and nearby blood vessels may lead to complications, including diminished sensation or the development of hematomas (2). Furthermore, research suggests that the ZFF has been utilized as an anthropological indicator to differentiate various populations and ethnic groups (8).

A thorough understanding of the anatomical variations of the ZFF, particularly its position and occurrence, may contribute to improved surgical outcomes while minimizing complications and iatrogenic injuries (9,10,11).

Therefore, this study aims to investigate the anatomical variations of the ZFF in a sample of adult dry skulls, employing selected morphometric methods. By analyzing the location, frequency, and relationship of the ZFF with surrounding structures, we seek to contribute valuable insights to improve surgical planning and minimize potential complications.

AIM

The aim of the study was to analyze the ZFF's shape, diameter, and location, as well as its spatial relationships with key anatomical landmarks.

MATERIALS AND METHODS

For this study, fifty - seven dry and well-preserved adult human skulls (114 hemicrania) of identified sex and age were examined. The specimens were obtained from the collection of the Institute of Anatomy, Faculty of Medicine, University of Sarajevo. A rigorous selection process ensured the exclusion of skulls exhibiting facial bone deformities, fractures, or any pathological abnormalities.

Our research methodology relied on established principles from previous studies, with certain modifications to enhance accuracy. Morphometric measurements were performed using both manual and digital Vernier calipers (Mitutoyo Co., Japan), ensuring precision up to 0.1 mm. Each measurement was taken twice on both sides of the skull, and the average value was recorded in millimeters. The collected data was systematically arranged in Microsoft Excel 2019© for further analysis.

Each skull was positioned in the Frankfort horizontal plane according to standardized procedures, followed by a detailed examination of the lateral surface of the zygomatic bone (ZB). The number of zygomaticofacial foramina (ZFF) was identified bilaterally. Measurements of both the vertical (VD) and transverse (TD) diameters of the zygomaticofacial foramen (ZFF) were conducted. The VD was recorded as the distance from the superior to the inferior margin of the foramen, whereas the TD was measured as the span between the medial and lateral margins. These measurements were carefully documented (Figure 1).

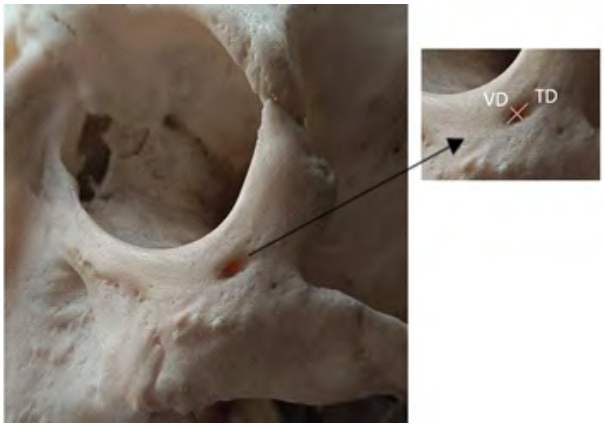


Figure 1 **ZFF diameters (TD - transverse diameter, VD - vertical diameter).**

The classification of the foramina was based on their vertical (VD) and transverse (TD) diameters, dividing them into two categories: the main zygomaticofacial foramen (mZFF) and accessory foramina (aZFF). The mZFF was identified as the foramen with the largest dimensions, while aZFF represented additional foramina on the same side. Furthermore, the shape of the mZFF was assessed based on the ratio of VD to TD, following these criteria:

- If the VD and TD values differed by less than 10%, the foramen was classified as round.
- If the difference ranged from 10% to 50%, the foramen was classified as oval.
- If the difference exceeded 50%, the foramen was classified as semilunar.

The location of the main zygomaticofacial foramen (mZFF) was assessed by measuring its distance to five key landmarks: the infraorbital margin (IOM), the midpoint of the frontozygomatic suture (FZS), the lowest point of the zygomaticomaxillary suture (ZMS), the midpoint of the zygomaticotemporal suture (ZTS), and the most prominent point on the zygomatic bone's lateral surface (ZP), (Figure 2).

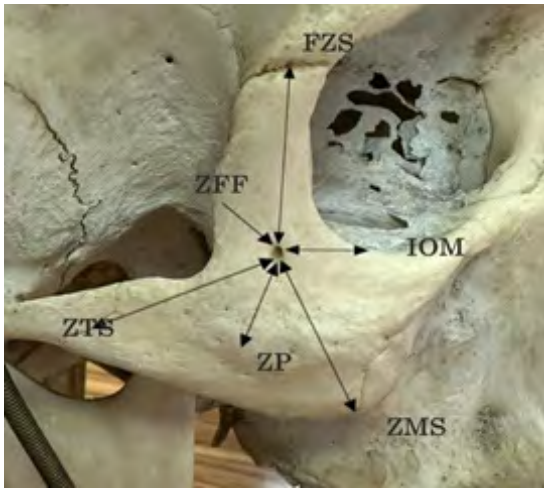
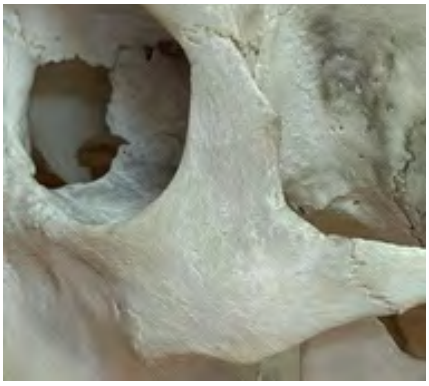


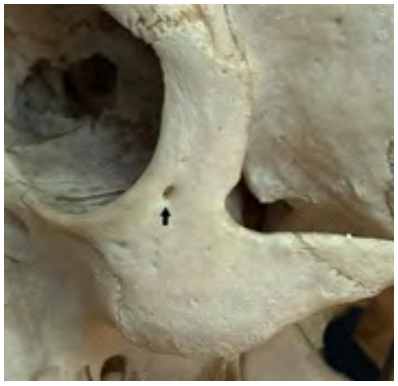
Figure 2 **The distances from the ZFF to the anatomical landmarks.**
ZFF-FZS, the distance from the ZFF to the frontozygomatic suture;
ZFF-ZMS, the distance from the ZFF to the lowest point of the zygomaticomaxillary suture; ZFF-IOM, the distance from the ZFF to the closest on the orbital margin; ZFF-ZP, the distance from the ZFF to the zygomatic prominence.

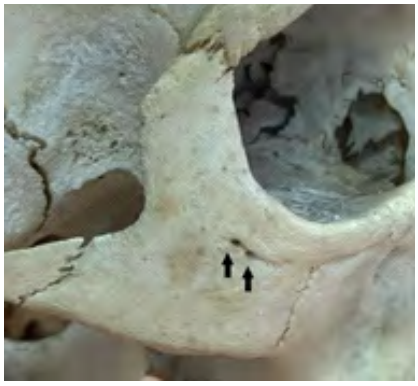
Statistical analysis was performed using IBM SPSS Statistics 28.0, applying standard methods such as mean, standard deviation, and range. The Chi-Square test and Fisher's Exact Test assessed categorical variable relationships, while the paired Wilcoxon Signed Ranks Test and paired t-test compared diameters and distances between skull sides. Statistical significance was set at $p \leq 0.05$.

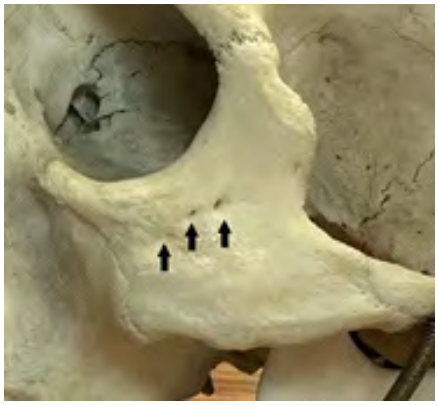
RESULTS

The zygomaticofacial foramen (ZFF) was identified in 55 out of the 57 examined skulls (114 hemicrania). All foramina located on the lateral surface of the zygomatic bone (ZB) were classified as ZFF and further divided into main ZFF (mZFF) and accessory ZFF (aZFF). A total of 112 mZFF and 86 aZFF were recorded across all samples. The number of ZFF per skull ranged from 0 to 5 (Figure 3).


Absence of ZFF


Single Foramen


Double Foramina


Triple Foramina


Four Foramina

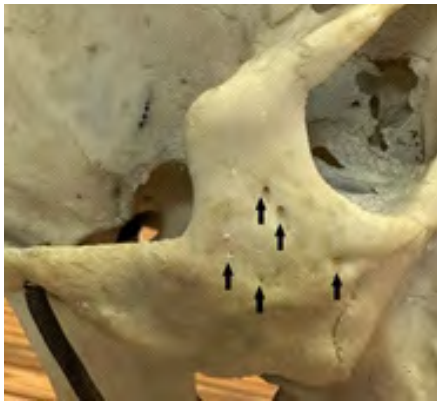

Five foramina

Figure 3 **The number of zygomaticofacial foramina.**

A single foramen was most common (40.4%), followed by two foramina (36.8%) (Table 1). There was a significant relationship between the numbers of foramina on the left and right sides ($P < 0.001$). Two skulls had no foramina on either side, while the third lacked it on only one side. In 34 skulls, the number of foramina was equal on both sides, while 23 showed asymmetry. More foramina were present on the right side in 18 skulls and on the left in 9 skulls, but this difference was not statistically significant ($P = 0.123$).

Table 1 **Distribution of the number of foramen in left and right hemicranias**

Side	Total (n = 114)		Right side (n = 57)		Left side (n = 57)	
Numbers	%	n	%	N	%	n
0	4.4	5	3.5	2	5.3	3
1	40.4	46	38.6	22	42.1	24
2	36.8	42	38.6	22	35.1	20
3	10.5	12	10.5	6	10.5	6
4	5.3	6	3.5	2	7.0	4
5	2.6	3	5.3	3	0	0

The mean VD of the ZFF was 0.83 ± 0.31 mm, ranging from 0.20 to 2.3 mm, while the average TD was 0.70 ± 0.29 mm, with a range of 0.28 to 2.70 mm (Fig. 5). In most cases (68.9%), VD was larger than TD, while TD was larger in 27.2%. Only 2.9% of cases had equal VD and TD values. A significant difference was found between left and right TD values ($P = 0.04$), but not for VD ($P = 0.68$).

Variations in the shape of the main zygomaticofacial foramen (mZFF) were identified, with the oval shape being the most prevalent (69%), followed by round (25.5%), semilunar (4.0%), and irregular (1.5%) (Fig. 6). Bilateral symmetry in mZFF shape was observed in 42 out of 57 skulls (73.6%). Statistical analysis revealed a significant correlation between the left and right sides concerning mZFF shape ($P < 0.001$).

The distances from the zygomaticofacial foramen (ZFF) to key surrounding anatomical landmarks were measured and are summarized in Table 2.

Table 2 **Measurements of distances from zygomaticofacial foramen to surrounding a nantomical landmarks (in mm).**

Measured parameter	Side	Samples	Mean±SD	Range	Confidence l interval (95%)	P-value
mZFF-IOM	Right	55	7.11 ± 2.15	3.98 - 13.34	6.59–7.65	0.55*
	Left	54	7.33 ± 2.44	3.34 - 14.34	6.70–7.96	
	Total	109	7.22 ± 2.29	3.34 - 14.34	6.75–7.59	
mZFF-FZS	Right	55	26.91 ± 3.52	20.84 - 35.37	25.98–27.83	0.8*
	Left	54	26.75 ± 3.90	18.09 - 34.59	25.71–27.79	
	Total	109	26.83 ± 3.69	18.09 - 35.37	26.15–27.51	
mZFF-ZMS	Right	55	20.05 ± 3.44	9.95 - 27.29	19.08–21.02	0.001*
	Left	54	20.62 ± 3.66	10.19 - 30.35	19.59–21.65	
	Total	109	20.34 ± 3.55	9.95 - 30.35	19.64–21.03	
mZFF-ZTS	Right	55	23.41 ± 4.51	13.86 - 33.70	22.21–24.61	0.02**
	Left	54	22.38 ± 3.84	12.51–28.69	21.35–23.38	
	Total	109	22.90 ± 4.18	12.51 -33.70	22.12–23.67	
mZFF-ZP	Right	55	8.52 ± 2.85	4.42 - 14.42	7.77–9.25	0.65**
	Left	54	8.72 ± 2.83	3-34 - 15.59	7.98–9.47	
	Total	109	8.62 ± 2.84	3.34 - 15.59	8.10–9.13	

*Wilcoxon Signed Ranks Test and paired t-test, **Paired t-test.

A statistically significant difference between the right and left sides was observed for the mZFF-ZMS distance (P = 0.001) and mZFF-ZTS distance (P = 0.03). However, no significant differences were found for the remaining measured distances (Figure 2).

This study identified 86 accessory zygomaticofacial foramina (aZFF), with the number per skull side varying between 1 and 4. The mean distance from mZFF to aZFF was 6.87 ± 3.39 mm, ranging from 1.09 mm to 21.00 mm. Statistical analysis showed no significant differences between the right and left sides (P = 0.32).

DISCUSSION

Understanding the zygomaticofacial foramen (ZFF) is essential for surgical procedures in this region. Previous research has examined the foramina using different methods, including dry skull assessments, isolated zygomatic bones, cadaver studies, and CT image analysis (2,3,5,6,7,8,11,12,13,14,15,16,17,18). Some studies have also compared measurements from physical skull examinations with those from CT scans (4). The variation in the number of foramina is mainly linked to embryological factors, particularly differences in the number of ossification centers in the zygomatic bone (11).

The presence of the zygomaticofacial foramen (aZFF) is a potential risk factor for neurovascular injury. Numerous studies have investigated the incidence and variation in the number of ZFFs, yielding different findings. Reported ranges include 0-3 (17), 0-4 (2,4,8,14,16,18,19), and 0-5 foramina (11,12,20). Chatzioglou N, et al. (9) recorded a maximum of six foramina, while Zhao Y, et al. (11) reported an average of 1.98 ± 0.93 foramina per specimen. The most frequently observed number was one, with an occurrence rate between 30.4% (9) and 53.3% (8). Two foramina were present in 12.12% (17) to 32.7% (16) of cases, consistent with our findings. Interestingly, previous studies have documented a higher percentage of cases without a foramen (up to 21.8%), while our study identified an absence rate of only 4.4%, which is closest to the result reported by Zhao Y, et al. (11). Notably, Mokryk O, et al. (19) did not find any cases of ZFF absence.

Research suggests that when the zygomaticofacial foramen (ZFF) is absent, the zygomaticofacial nerve may also be missing. In these cases, sensory input to the malar region is maintained by other branches of the trigeminal nerve (18). Several studies have examined foramen distribution based on ethnicity, sex, and skull structure. While some have reported notable sex-related differences (16), others have found no statistically significant variation between male and female skulls (8,7).

The diameter of the zygomaticofacial foramen (ZFF) is an essential metric in determining the likelihood of nerve injury during facial surgeries. By analyzing its size, we can approximate the dimensions of the nerves that pass through it. Research has established a connection between foramen diameter and the risk of nerve paresthesia (11).

Our study estimated the vertical (VD) and transverse (TD) diameters of the zygomaticofacial foramen (ZFF) at 0.83 ± 0.31 mm and 0.70 ± 0.29 mm, respectively. In comparison, Del Neri NB, et al. (4) reported an average ZFF diameter of 0.57 ± 0.27 mm, while Carvalho C, et al. (13) documented a range of 1.083-1.108 mm in males and 1.077-1.092 mm in females. Diameter variations from 0.3 to 1.85 mm have been noted (6). Kawata et al. (16) analyzed 52 cadavers and found mean ZFF diameters of 1.09 mm in males and 1.03 mm in females, with no significant differences between sexes. Coutinho DC, et al. (6) identified a larger VD on the left side but found no relationship between VD and TD.

Evaluating the shape of the zygomaticofacial foramen (ZFF) is crucial for precise anesthetic block administration (6). Coutinho DC, et al. (6) reported that circular foramina were the most frequent (63.9% right, 50.8% left), with oval ones following closely (36.1% right, 49.2% left).

Our study, however, found the oval shape to be the most dominant (69%), with circular foramina in 25.5% of cases. Unlike previous findings, we also observed semilunar foramina in 4.0% of cases, highlighting anatomical variability.

Precise localization of the zygomaticofacial foramen (ZFF) is crucial in facial surgery. Our study investigated its spatial relationship with clinically significant anatomical landmarks, including the infraorbital margin (IOM), frontozygomatic suture (FZS), zygomaticomaxillary suture (ZMS), and zygomaticotemporal suture (ZTS), as highlighted in prior research (6,9,12). Our findings revealed an average ZFF-IOM distance of 7.22 ± 2.29 mm, corroborating the data reported by Chatzioglou N, et al. (9). Literature values for this distance range from 1.2 to 11 mm (2,15), with Deana NF, et al. (8) noting positional variability. Regarding the ZFF-FZS distance, our study established an average of 26.83 ± 3.69 mm, similar to Aksu F, et al. (12). Comparative studies reported slight differences, with Hwang et al. (14) recording a mean of 24.4 mm and Coutinho DC, et al. (6) documenting 27.49 mm.

Previous research has reported that the distance between the zygomaticofacial foramen (ZFF) and the zygomaticomaxillary suture (ZMS) ranges from 17.50 mm to 20.05 mm (6,17). Our study found an average distance of 20.34 ± 3.55mm. The ZFF-ZTS distance measured 22.90 ± 4.18 mm, aligning with Coutinho DC, et al. (6). Several studies have examined ZFF distances from other anatomical landmarks. Hwang SeHo, et al. (14) noted that the ZFF was positioned 7.3 mm laterally and 3.7 mm inferiorly from point P, where a line along the upper zygomatic arch intersects a vertical line on the lateral orbital rim. Additionally, the ZFF was located 11.0–13.0 mm from the zygomatic angle (3,14).

A major question in facial surgery is how to accurately locate the ZFF in living individuals. Our study examined this by measuring its position relative to the ZP, a prominent point on the zygomatic bone. The ZFF was, on average, 8.62 ± 2.84 mm from the ZP, with distances ranging from 2.85 to 15.7 mm.

Surgical procedures in the zygomatic region carry an increased risk of nerve damage due to the presence of aZFF. Previous studies (3,12) have highlighted this risk, advising surgeons to exercise caution. To date, only one study has specifically examined the spatial relationship between aZFF and the primary zygomaticofacial foramen. Martins C, et al. (3) reported that in cases of multiple foramina, they were positioned along a line parallel to the orbital margin, with an average distance of 0.5 cm (range: 0.1–1.3 cm). Our findings indicate that the average distance between mZFF and aZFF is 6.87 ± 3.39 mm, ranging from 1.09 mm to 21.00 mm. Although precise data on aZFF location remain scarce, this information may aid in surgical planning and reduce the likelihood of nerve injury.

CONCLUSION

The clinical relevance of the zygomatic region is shaped by the presence and contents of the ZFF. Given its variability in number and location, careful consideration is essential when performing regional anesthesia, surgical procedures, or aesthetic treatments near the infraorbital margin. Ignoring these variations may lead to complications that could otherwise be prevented. By providing an in-depth analysis of the ZFF's morphology, positioning, and anatomical associations, our study offers valuable contributions to clinical medicine.

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Ipsilateral Total Hip Arthroplasty in 74-Year Old Above-Knee Amputee

Ipsilateralna ugradnja totalne endoproteze kuka kod 74-godišnjeg muškarca sa natkoljenom amputacijom

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ABSTRACT

Introduction: amputation of lower extremities is one of the biggest disabilities around the world. There is a great number of lower limb amputees in Bosnia and Herzegovina. Total hip replacementin ipsilateral above-knee amputation is described in literature. Case report: 74-year old male with above knee amputation was treated with total hip replacement on Clinic of Ortopedcis and Traumatology of the Clinicial Center University of Sarajevo. Postoperatively after complete wound healing patient was able to use previously prescribed prosthetic and to return to daily activities. Conclusion: ipsilateral total hip replacement was made successfully to above-knee amputee. Postoperative follow-up showed that choice of treatment was correct and successfull, as well as enabling patient to return to daily activities.

Keywords: amputation, total hip replacement, ipsilateral, above-knee prosthetic, femoral neck fracture

SAŽETAK

Uvod: amputacija donjeg ekstremiteta predstavlja jedan od najtežih oblika invalidnosti širom svijeta. Na području Bosne i Hercegovine postoji veliki broj pacijenata sa amputiranim donjim ekstremitetom. Ugradnja totalne endoproteze kuka kod pacijenata sa ipsilateralnom natkoljenom amputacijom je opisana u literaturi. Prikz slučaja: pacijentu, muškog spola, u dobi od 74 godine sa natkoljenom amputacijom donjeg desnog ekstretmiteta je ugrađena endoproteza desnog kuka na Klinici za ortopediju i traumatologiju KCUS. Zaključak: postoperativno nakon potpunog cijeljenja rane pacijentu je omogućeno da nosi ranije korištenu protezu, te povratak svakodnevnim aktivnostima.Pacijentu je uspješno ugrađena totalna endoproteza kuka na strani natkoljene amputacije. Postoperativno praćenje je ukazalo na pravilan odabir i uspješnost tretmana, te da je navedeno dovelo do poboljšanja kvaliteta života pacijenta.

Ključne riječi: amputacija, endoproteza kuka, ipsilateralna, natkoljena proteza, prelom vrata femura

INTRODUCTION

Amputation of the lower limb is one of the most severe forms of disability worldwide. Considering the war that took place in Bosnia and Herzegovina, there is a large number of patients with amputated lower limbs. Unfortunately, there is no accurate record of how many patients in Bosnia and Herzegovina have had one or both lower limbs amputated. Over the years, the incidence and prevalence of traumatic amputations increased by 16.4% and 49.2%, respectively (1). It is estimated that in 2021 there were 57.7 million people in the world who had their lower limb amputated as a result of an injury, of which the most common cause was falls in 36.2%. cases, and traffic injuries in 15.7% of cases (2).

CASE REPORT

A 74-year-old male patient came to the CCUS Orthopedics and Traumatology Clinic after an injury to his right hip caused by a fall from the same level onto a hard surface. Earlier, in 1992, he underwent transfemoral amputation of the right lower extremity after injury. The aforementioned injury was treated, and the patient regularly used a prosthesis for the right lower limb. Upon admission, a radiological evaluation was performed, which showed a fracture of the neck of the right femur (Figure 1). The patient was offered treatment options, and the patient agreed to the surgical treatment of implanting a total endoprosthesis (TEP) of the right hip. Upon admission of the patient to the department, preoperative preparation was carried out, and the patient underwent operative treatment.

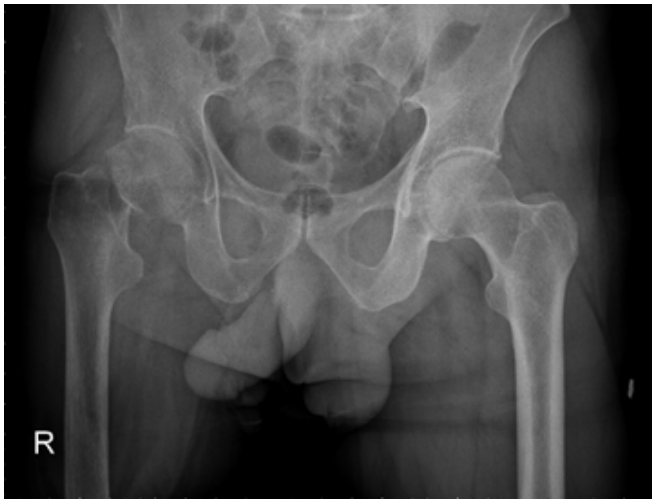

Figure 1 **Preoperative pelvis radiographic image**.

The operation was performed under general endotracheal anesthesia. The patient was placed in a dorsal decubitus position, and the lateral approach to the right hip was chosen as the access method. Upon access to the neck of the femur, a fracture crack was shown, which corresponded to the preoperative diagnosis. The head was removed, and then the acetabulum was presented, which was then prepared for the acetabular component, after which it was placed with medical cement. Then the femur was presented, and the canal was prepared for the stem, which was placed along with medical cement. Intraoperatively, the size of the head of the endoprosthesis was determined, which was then placed on the stem. After the endoprosthesis was repositioned, clinical stability tests were performed, which showed that the placed prosthesis was stable. The wound was then closed in layers with the placement of aspiration drainage.

The operative course was uneventful, as was the awakening from anesthesia, and the patient was transferred to the ward. The control X-ray showed the correct position of the endoprosthesis (Figure 2).

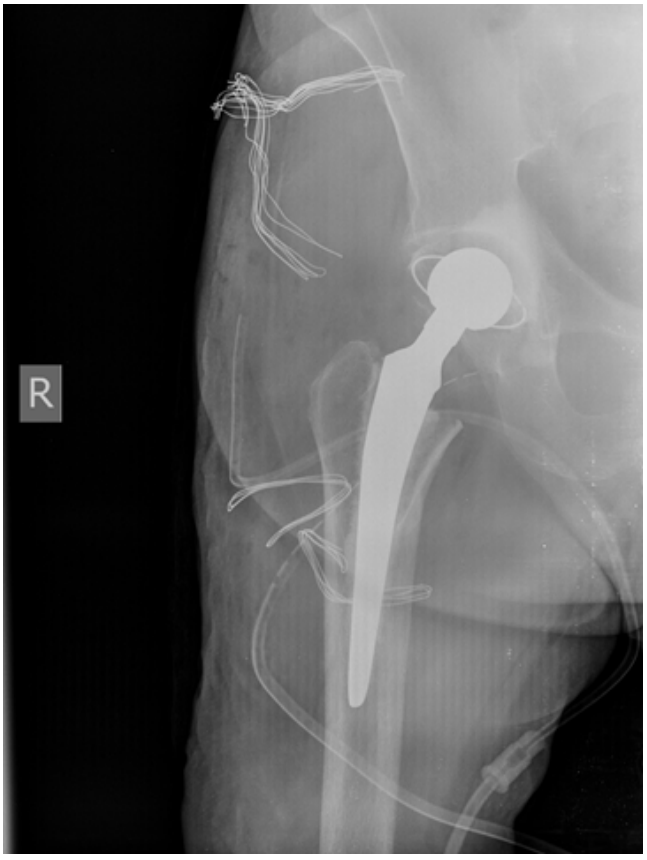

Figure 2 **Postoperative pelvis radiographic image**.

On the first postoperative day, physical rehabilitation was started. Aspiration drainage was removed on the second postoperative day. Considering the upper leg amputation, it was decided not to return the upper leg prosthesis until the postoperative wound has healed.

On the seventh postoperative day, the patient was discharged from the CUS Orthopedics and Traumatology Clinic for home treatment. During the control examination, on the fifteenth postoperative day, it was determined that the wound had healed properly, and that there were no signs of edema or inflammation, and the sutures were removed.

At the follow-up examination, one month after the operation, an X-ray of the pelvis and hips was performed, which showed the proper position of the endoprosthesis (Figure 3). Given that the wound was properly healed, previously used lower limb prosthesis was applied, and the patient was instructed to wear it with full weight-bearing and also to use crutches. According to the protocol, the patient was sent to spa physical treatment for the continuation of rehabilitation.

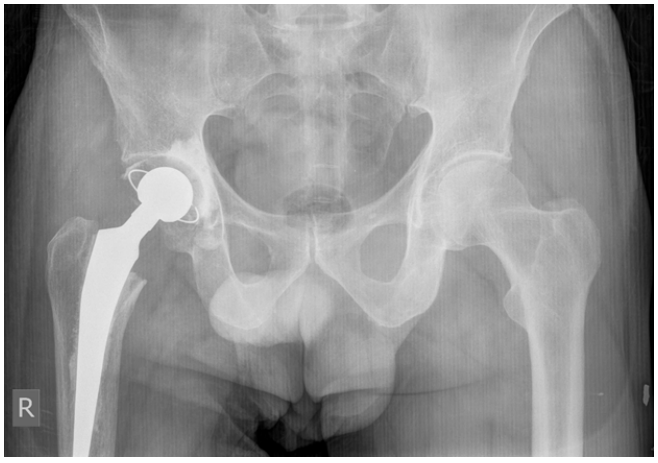

Figure 3 **Pelvis radiographic image at follow-up one month after the surgery**

The rehabilitation was successfully completed six months after the operation, and the patient was able to use the lower leg prosthesis that he used before the injury, without the help of crutches.

DISCUSSION

A systematic review conducted in 2023, which included 40 studies indexed in MEDLINE, Cochrane Library, EMBASE, and CINAHL, and which mostly consisted of case reports and case series reports, determined that the most common cause of endoprosthesis implantation in patients with lower extremity amputation was osteoarthritis (77.1%), and that in 66.7% of cases it was present on the contralateral limb (3). Existing studies related to the implantation of an endoprosthesis after amputation of the lower limb have shown that the implantation of a total hip endoprosthesis on the ipsilateral side results in a slightly lower number of complications than the implantation on the contralateral side (4-9).

CONCLUSION

The patient was successfully implanted with a total hip endoprosthesis on the side of the lower leg amputation. Postoperative follow-up indicated the correct selection and success of the treatment, and led to an improvement in the patient's quality of life.

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Vaginal Leiomyoma in a Perimenopausal Woman

Vaginalni leiomiom kod žene u perimenopauzalnom periodu

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ABSTRACT

Introduction: vaginal leiomyomas are rare, benign tumors that most commonly occur during the reproductive period, affecting 20 to 30% of women. The final diagnosis is made through histopathological examination. Case report: we present the case of a 58-year-old woman who presented to the clinic with a tumor on the vulva. A gynecological examination revealed the presence of a mass that slightly protruded into the lower third of the vagina near the vaginal introitus. The surgery began with an incision in the vulvar area, which was extended into the vagina due to the unexpected depth of the tumor. Histopathological examination confirmed the diagnosis of a vaginal leiomyoma. Conclusion: the presented case highlights the rarity and nonspecific nature of vaginal leiomyomas and helps raise awareness about them.

Keywords: vaginal leiomyoma, case report

SAŽETAK

Uvod: vaginalni leiomiomi su rijetki, benigni tumori koji se najčešće javljaju tokom reproduktivnog perioda i zahvataju 20 do 30 % žena. Konačna dijagnoza postavlja se patohistološkom analizom. Prikaz slučaja: prikazujemo slučaj 58-godišnje žene koja se na kliniku javila zbog tumora na vulvi. Ginekološkim pregledom utvrđeno je prisustvo mase koja blago protrudira u donju trećinu vagine, u blizini introitusa vagine. Operacija je započeta rezom u području vulve, a zbog neočekivane dubine tumora proširena je na vaginu. Patohistološkom analizom uspostavljena je dijagnoza vaginalnog leiomioma. Zaključak: prezentovani slučaj pokazuje rijetkost i nespecifičnost vaginalnih leiomioma i pomaže u podizanju svijesti o njima.

Ključne riječi: vaginalni leiomiom, prikaz slučaja

INTRODUCTION

Vaginal leiomyoma is a benign tumor of the female genital tract (1). The first case was documented by Denys de Leyden in 1733, and only 300 cases have been reported since (2,3). Leiomyomas affect 20 - 30% of women of reproductive age but leiomyomas occurring primarily in the vagina are rare (3). They may or may not be associated with leiomyomas elsewhere in the body (4). Vaginal leiomyomas are typically round, well-circumscribed, whorl-like, and can be intramural or pedunculated (1).

Vaginal leiomyoma can be found on the anterior vaginal wall (69.5%), on the posterior (17%) and lateral walls (13.5%). They can either be asymptomatic or accompanied by symptoms such as pelvic pressure, vaginal bleeding, dyspareunia, abdominal pain, dysuria and urinary issues like voiding dysfunctions and they can cause various symptoms or even have an impact on nearby organs like the bladder, rectum, uterine cervix, or vulva (5).

The condition is of interest because of its rarity and of importance because of the unusual problems which may arise in connection with its diagnosis. Because of the variety of sizes, appearances and locations of vaginal myomas, the condition has been variously mistaken for sarcoma, carcinoma, vaginal cyst, uterine prolapse, cystocele and adenomyoma of the vagina (2). Careful assessment is required for clinical diagnosis. The diagnosis is usually confirmed through histopathological examination (6).

We present the case of a perimenopausal woman who presented with a mass in the vulvar area, which, upon further investigation, was diagnosed as a vaginal leiomyoma.

CASE REPORT

A 58 - year - old woman, gravid 3, para 2, was referred to our clinic due to a vulvar mass close to vaginal introitus. The change occurred 6 months prior to the visit, accompanied by redness of the vulva, which was treated. The patient reports a change located near the vaginal introitus, which slightly protrudes into the inner part of the vagina and a feeling of pressure in that area. The patient has no other gynecological issues, nor allergies to food or medications, and is otherwise healthy. In 2014, she underwent surgery for breast cancer (follow-up tests are normal).

The gynecological examination revealed a finding at the entrance of the vagina, in the lower third, a palpably firm lobulated formation the size of a walnut is found, with no local change in skin color, and is painless to the touch. Diagnostic imaging was not performed. The preoperative preparation is completed successfully, without issues.

After the preoperative preparation and the induction of general anesthesia, a vulvar incision is made, 1 cm laterally from the right labia majora in the perineal border region. After that, the tumor excision is performed; however, it is noted that the tumor is located deep and along the lateral wall of the vagina.

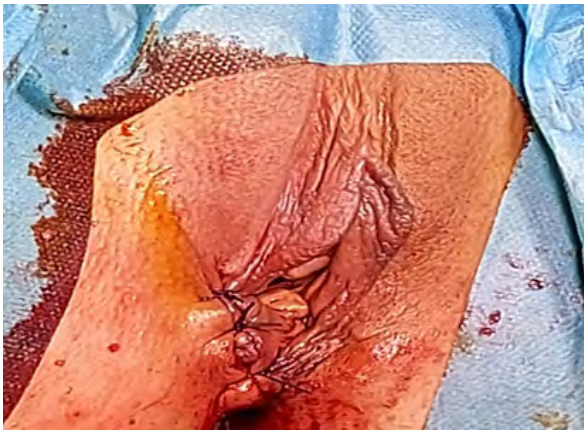

Figure 1 **The location of tumor extraction.**

As a result, the tumor was approached through the vagina and completely removed. A tumor mass measuring 46 x 42 x 23 mm was obtained, with an irregular and papillary appearance, along with several smaller fragments. After the tumor removal, the lateral vaginal wall and the incised vulvar area were closed. The obtained material was sent for histopathological analysis which revealed a vaginal leiomyoma.

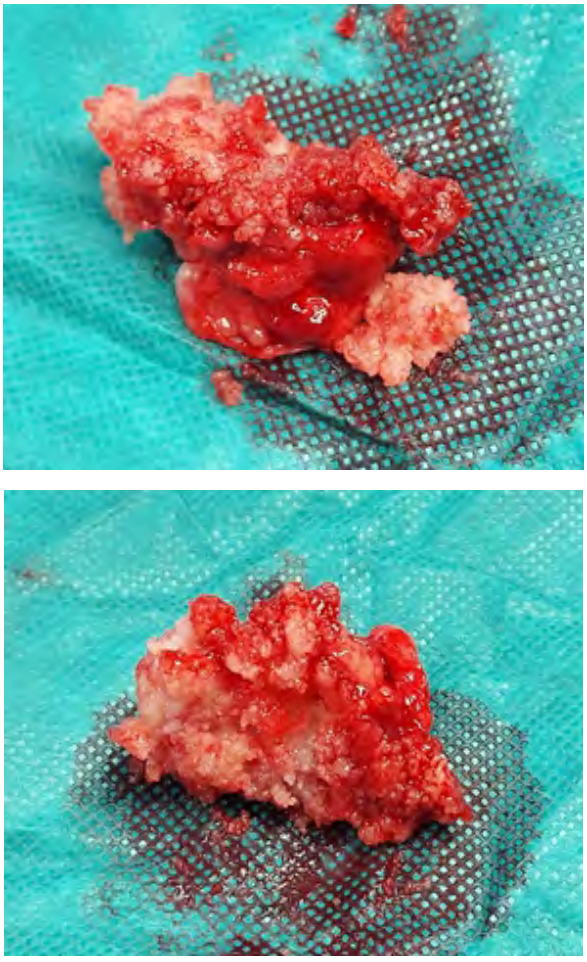

Figure (2,3) **Histopathological specimen.**

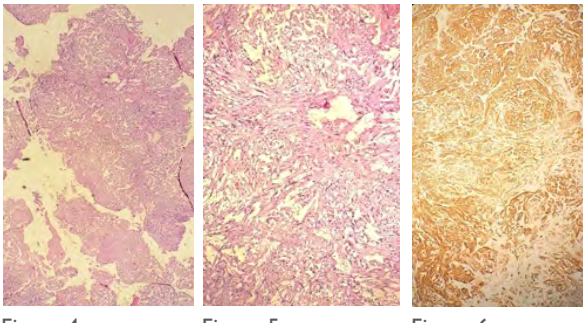

Figure 4 Figure 5 Figure 6

Figure (4,5,6) **Microscopic view of the specimen.**

DISCUSSION

Ectopic leiomyoma is a rare, benign tumor originating from smooth muscle tissues that can be found in various locations, such as the ovary, round ligament, broad ligament, and, in rare cases, the vulva and vagina (4). Vaginal leiomyomas most commonly occur in women aged 35 to 50, which makes the case we presented particularly interesting, as the patient is 58 years old (3).

A study by Bennett HG, et al., revealed an extremely low incidence of vaginal leiomyoma. Out of 50,000 samples analyzed through histopathological examination, only nine cases were identified. Among the 15,000 autopsies performed at Johns Hopkins Hospital, only one case of vaginal leiomyoma was reported (2).

Vaginal leiomyomas are most often asymptomatic or associated with symptoms such as pelvic pressure, vaginal bleeding, dyspareunia, abdominal pain, dysuria and urinary issues like voiding dysfunctions (4), and in our case, the patient reported pressure in the vulvar area and the lower third of the vagina. Vaginal leiomyoma can be found on the anterior vaginal wall (69.5%), on the posterior (17%) and lateral walls (13.5%), (4) the case we presented involves a lateral presentation of a vaginal leiomyoma, making it the rarest type. Usually, they present as a smooth, firm, round mass whereas in our case, the mass has an uneven and papillary appearance.

Treatment for vaginal leiomyomas varies depending on the location and size of the leiomyoma. The preferred treatment is vaginal excision. Unlike conventional vaginal surgery, vaginal myomectomy performed via transvaginal natural orifice transluminal endoscopic surgery (vNOTES) offers a clearer approach and potentially better outcomes (1).

CONCLUSION

Vaginal leiomyomas are rare, benign tumors whose clinical presentation depends on the location of the tumor. The final diagnosis is made through histopathological analysis, while prior to that, appropriate diagnostics such as ultrasound and pelvic MRI should be performed, if possible. Complete excision of the tumor is the most appropriate and definitive treatment option

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Recurrent Hemoptysis in a 3-Month-old Infant: a Diagnostic Challenge Leading to the Discovery of a Nasal Angiofibroma

Rekurentna hemoptiza kod tromjesečnog dojenčeta: dijagnostički izazov koji vodi do otkrića angiofibroma nosa

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ABSTRACT

Introduction: hemoptysis in infants is a rare condition that presents significant diagnostic challenges. Nasal angiofibromas are benign vascular tumors that typically occur in adolescent males, with less than 0.1% of cases reported in infants under one year of age, making their diagnosis particularly challenging in this age group. Aim: to present a unique case of nasal angiofibroma in a 3-month-old infant presenting with recurrent hemoptysis. Case report: A 3-month-old male infant initially admitted for urinary tract infection developed unexplained hemoptysis during hospitalization. Despite extensive diagnostic workup, the etiology remained unknown for an extended period, partly due to the parents' initial refusal of bronchoscopy. Further evaluation at the Institute for Mother and Child in Belgrade revealed angiofibroma in the nasal cavity as the source of bleeding. The condition was successfully treated using APC (argon plasma coagulation) electrocauterization, demonstrating the effectiveness of minimally invasive approaches in managing these rare lesions. Conclusion: this case represents one of the youngest reported instances of nasal angiofibroma in medical literature, highlighting the importance of considering rare vascular tumors in the differential diagnosis of infant hemoptysis. The successful management through a multidisciplinary approach and minimally invasive intervention provides valuable insights for similar cases, while emphasizing the need for further research into optimal management strategies for nasal angiofibromas in infants.

Keywords: hemoptysis, nasal angiofibroma, coagulation, APC, electrocauterisation, obstruction of respiratory tract

SAŽETAK

Uvod: hemoptiza kod novorođenčadi je rijetko stanje koje predstavlja značajne dijagnostičke izazove. Nazalni angiofibromi su benigni vaskularni tumori koji se obično javljaju kod adolescentnih muškaraca, sa manje od 0,1% slučajeva prijavljenih kod dojenčadi mlađe od godinu dana, što njihovu dijagnozu čini posebno izazovnom u ovoj starosnoj grupi. Cilj: prikaz jedinstvenog slučaja angiofibroma nosa kod tromjesečnog dojenčeta sa rekurentnom hemoptizom, naglašavajući dijagnostičke izazove, multidisciplinarni pristup i važnost razmatranja rijetkih etiologija hemoptize dojenčadi. Prikaz slučaja: 3-mjesečno novorođenče koje je prvobitno primljeno zbog infekcije urinarnog trakta razvilo je neobjašnjivu hemoptizu tokom hospitalizacije. Unatoč opsežnoj dijagnostičkoj obradi, etiologija je ostala nepoznata duži period, dijelom zbog prvobitnog odbijanja bronhoskopije od strane roditelja. Daljom procenom na Institutu za majku i dete u Beogradu utvrđen je angiofibrom u nosnoj duplji kao izvor krvarenja. Stanje je uspješno liječeno elektrokauterizacijom APC (argon plazma koagulacije), demonstrirajući efikasnost minimalno invazivnih pristupa u liječenju ovih rijetkih lezija. Zaključak: ovaj slučaj predstavlja jedan od najmlađih prijavljenih slučajeva angiofibroma nosa u medicinskoj literaturi, naglašavajući važnost razmatranja rijetkih vaskularnih tumora u diferencijalnoj dijagnozi hemoptize dojenčadi. Uspješno liječenje multidisciplinarnim pristupom i minimalno invazivnom intervencijom daje vrijedan uvid u slične slučajeve, naglašavajući potrebu za daljnjim istraživanjem optimalnih strategija liječenja nazalnih angiofibroma kod dojenčadi.

Ključne riječi: hemoptiza, angiofibrom nosa, koagulacija, opstrukcija dišnog puta, APC, elektrokauterizacija

INTRODUCTION

Hemoptysis in infants is a rare but potentially life-threatening condition that presents significant diagnostic and therapeutic challenges. The differential diagnosis is broad, including infectious, structural, and hematological disorders. However, nasal angiofibroma as a cause of hemoptysis in infants is exceptionally rare, with few cases reported in the literature (1,2). Nasal angiofibromas are benign but locally aggressive vascular tumors that typically occur in adolescent male (3). Globally, they account for approximately 0.05% of all head and neck tumors, with an estimated incidence of 1 in 5,000 to 1 in 60,000 otolaryngology patients. Their occurrence in infants is exceptionally rare, with less than 5% of cases reported in patients younger than 10 years old. This rarity often leads to delayed diagnosis and management. The vast majority (about 95%) of cases occur in males aged 14-25 years, with a mean age at diagnosis of around 15 years (4,5,6). In our Pediatric Clinic of the Clinical Center University of Sarajevo, this case represents the first documented nasal angiofibroma in an infant presenting with hemoptysis. Nasal angiofibroma is characterized by a rich blood supply, suggesting that vascular changes might be involved in its growth. While the precise cause remains unclear, hormonal and genetic factors, along with environmental influences, are thought to play significant roles in the development of nasal angiofibroma.

AIM

The aim of this paper was to present a unique case of nasal angiofibroma in a 3-month-old infant presenting with recurrent hemoptysis, highlighting the diagnostic challenges, multidisciplinary approach and the importance of considering rare etiologies in infant hemoptysis.

CASE REPORT

A 3-month-old male infant was admitted to the Pediatric Clinic of the CCUS with a two- day history of fever (up to 39.7°C), decreased appetite, and irritability. The mother reported changes in urine color and odor. Initial laboratory findings showed elevated inflammatory markers (CRP 104.5 mg/L, WBC 19.9 x 10^9/L) and urinalysis suggestive of urinary tract infection. Blood and urine cultures were tested, E. coli was found in the urine culture so the patient was started on intravenous cefazolin. On the fifth day of hospitalization, while the initial infection was resolving, the infant began experiencing episodes of the fresh blood usually found on the pillow, next to patients head or in the mouth. The episodes occurred 1-2 times daily, often during sleep, and without associated coughing. This presentation is unusual for nasal angiofibroma, which typically present with epistaxis rather than hemoptysis.

The occurrence of nasal angiofibroma in a 3-month-old infant is exceptionally rare. While exact statistics for infants are not available due to the extreme rarity, a comprehensive review found that less than 0.1% of all reported nasal angiofibroma cases occurred in children under one year of age. This makes our case particularly important and potentially one of the youngest reported in the literature. Diagnostic workup was initiated, following the systematic approach for evaluating hemoptysis in children: Gastrointestinal evaluation: upper endoscopy revealed gastric erosions in the healing phase. The patient was treated with omeprazole. Respiratory evaluation: chest X-ray showed peribranchial opacities suggestive of bronchiolitis. MRI of the larynx, mediastinum, and thorax showed no significant abnormalities. Hematological evaluation: coagulation studies, including factor assays, were largely within normal limits for the patient's age. Infectious disease workup: multiple gastric lavage samples were tested for tuberculosis, with one sample growing Streptococcus viridians, treated with oral ampicillin. Otolaryngological and maxillofacial evaluations: Initial examinations showed no evident source of bleeding in the upper respiratory or digestive tracts. Neurological evaluation: MRI and MRA of the cranium showed no signs of altered signal intensity zones.

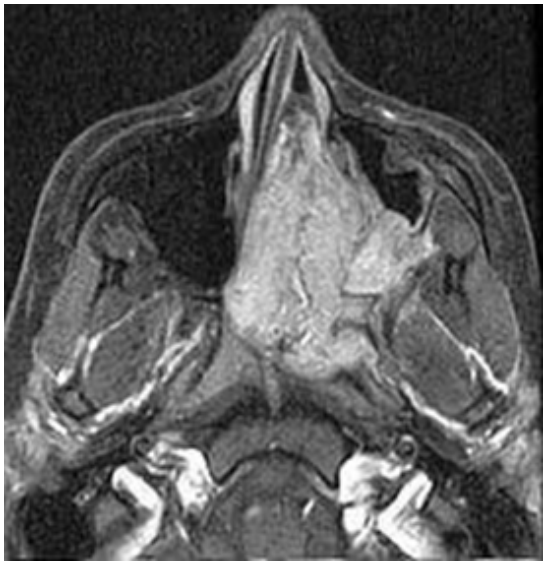

Figure 1 **MRI nasal angiofibroma (10).**

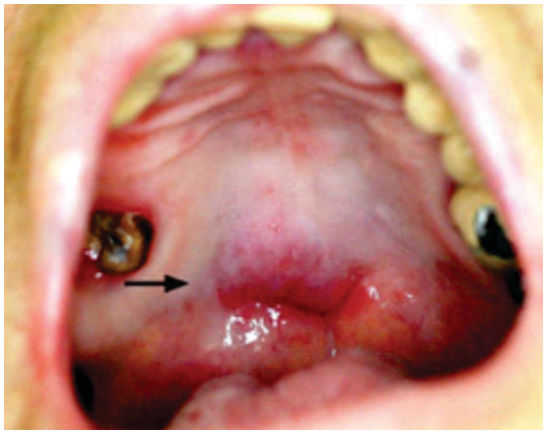

Figure 2 **Nasal angiofibroma (11)**.

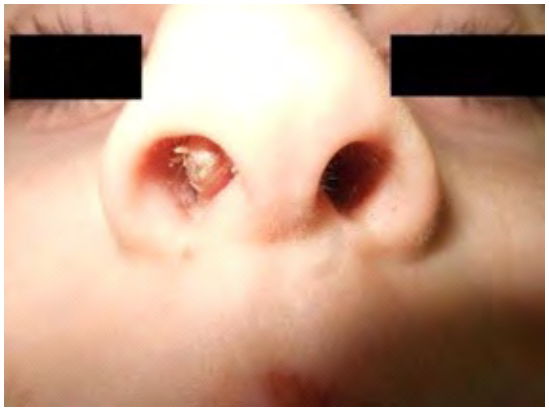

Figure 2 **Nasal angiofibroma (12)**.

The diagnostic procedure performed in Belgrade revealed a globular soft tissue tumefaction on the medial side of the anterior nasal passages, which bled easily on contact with the instrument. The discovery of the nasal mass was crucial in directing further diagnostic efforts towards a potential nasal angiofibroma, a diagnosis that had not been initially considered due to its extreme rarity in this age group. Following the bronchoscopy, an ENT specialist of the Institute for mother and child in Belgrade examination confirmed the presence of a vascular lesion in the nasal cavity, consistent with a nasal angiofibroma. Electrocauterization of the nasal concha was performed bilaterally using an APC attachment to address the epistaxis. The procedure was completed without complications, demonstrating the effectiveness of minimally invasive approaches in managing these lesions, as supported by recent literature. Follow-up evaluations, including a rhinopharyngoscopy showed significant reduction in the size of the lesion. Four weeks post- intervention, the child showed marked improvement with only minimal, occasional bleeding.

DISCUSSION

This case of nasal angiofibroma in a 3-month-old infant presenting with hemoptysis is rare, both in global literature and in our local experience at the pediatric clinic Clinical center Sarajevo. The rarity of this condition in infants contributed to the initial diagnostic challenge, as nasal angiofibromas are typically associated with adolescent males (7).

The case highlights several important points: rarity and diagnostic challenge: nasal angiofibroma is extremely uncommon in infants. A recent systematic review found no reported cases in infants under 6 months of age, making our case potentially the youngest reported in literature. The global incidence of nasal angiofibroma is approximately 0.05% of all head and neck tumors, with less than 0.1% of these cases occurring in infants under one year of age. Management approach: the successful use of electrocauterization in our case demonstrates the potential of minimally invasive techniques in managing nasal angiofibromas in infants (8). This is particularly relevant given the challenges of more aggressive interventions in this age group (9). Long-term considerations: while our patient showed significant improvement post- intervention, the long-term prognosis and potential for recurrence remain uncertain. Juvenile nasopharyngeal angiofibromas can have varying outcomes over extended periods, emphasizing the need for long-term follow-up. Infant with the nasal angiofibroma might develop nasal obstruction and difficulty breathing, feeding difficulties, weightloss, epistaxis, facial deformities, sleep disturbances and apnea, hearing loss, proptosis, impaired vision, or pressure on the optic nerve, leading to visual disturbances. If the tumor grows agressively it could invade the skull base and extend toward the brain, potentially leading to neurological complications like seizures, developmental delays, or behavioral changes. It can lead to higher incidence of sinus infection, or general developmental delays cause by difficulty breathing or feeding. Importance of the follow up: Complications of electrocauterization include continued bleeding due to incomplete cauterization, infection, damage to surrounding tissue, or underlying clotting disorders. Persistent bleeding can lead to anemia, hypovolemic shock, scarring, and airway obstruction in severe cases. Infection may also occur, and repeated attempts to control bleeding can result in further tissue damage. If electrocauterization fails, additional treatments like embolization, surgical intervention, or the use of hemostatic agents may be required to control the bleeding.

CONCLUSION

This case report presents a unique case of nasal angiofibroma in a 3-month-old infant, manifesting primarily as hemoptysis. It is the first case like this documented in our pediatric clinic in Sarajevo and potentially one of the youngest cases reported in global literature. Given that less than 0.1% of Nasal angiofibromas occur in infants, and that these tumors account for only 0.05% of all head and neck tumors, the rarity of this case cannot be overstated. The case highlights the importance of considering rare etiologies in the differential diagnosis of infant hemoptysis. The successful management of this case through a multidisciplinary approach and minimally invasive intervention provides valuable insights for similar cases in the future. However, it also highlights the need for further research into the long-term outcomes and optimal management strategies for nasal angiofibromas in infants. This is particularly important given that over 95% of cases typically occur in adolescent males, and our understanding of the condition in infants is limited.

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Encephalopathy Caused by Bartonella Henselae

Encefalopatija uzrokovana Bartonellom Henselae

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ABSTRACT

Introduction: encephalopathy refers to qualitative and quantitative disorders of consciousness due to brain dysfunction and is caused by a generalized brain injury or a focal lesion. Bartonellosis is a term used to describe infectious diseases caused by strains of Bartonella henselae, including cat-scratch disease. Neurological manifestations of these infections are very rare, especially in patients who are not immunocompromised. Case report: we present a 6-year-old boy, with no previous illnesses, who was hospitalized at the Pediatric Clinic following a diagnosis of status epilepticus. Upon admission, he was intubated. According to the medical history given by his caregivers, the boy had been scratched by a cat one month before hospitalization. This incidence was followed by symptoms such as headaches, nausea, fever and swollen peripheral lymph nodes. Upon admission, laboratory and radiology diagnostics were conducted, as well as an emergency fundus examination. All tests were clear. Lumbar puncture was performed on two occasions, both blood cultures and cerebrospinal fluid cultures were normal. The treatment of this complex case included multidisciplinary approach by an infectious disease specialist, an intensive care team, a neuropediatrician, an immunologist, a cardiologist, a gastroenterologist and a radiologist. They decided on a conservative approach and started antibiotics and symptomatic therapy, with monitoring. On the fourth day of hospital stay, the patient was extubated, vital signs were continuously monitored, remaining stable in the following days. After consulting with neuropediatricians on the ninth day of hospital stay, the patient was transferred to the Department of Neuropediatrics for further diagnostic evaluation and treatment. Conclusion: this case report highlights the importance of considering bartonellosis as a potential cause of neurological symptoms and outcomes. Key factors for improving the outcome of patients with encephalopathy are early identification of the cause, timely treatment, as well as a multidisciplinary approach due to the complexity of the diagnosis.

Keywords: encephalopathy, Bartonella henselae, status epilepticus, bartonellosis, cat scratch disease

SAŽETAK

Uvod: encefalopatija je pojam koji se odnosi na kvalitativne i kvantitavne poremećaje nivoa svijesti zbog disfunkcije moždanog tkiva, te može biti uzrokovana globalnim moždanim inzultom ili fokalnom lezijom. Bartoneloza je izraz koji se koristi za opisivanje zaraznih bolesti koje uzrokuju sojevi bakterije Bartonella henselae, uključujući i bolest mačijeg ogreba. Neurološke manifestacije pri infekciji su vrlo rijetke, posebno kod pacijenata koji nisu imunokompromitovani. Prikaz slučaja: dječak u dobi od 6 godina, bez ranijih oboljenja, hospitalizira se na pedijatrijsku kliniku pod dijagnozom Status epilepticus. Nakon prijema postavi se na kompletnu mehaničku ventilaciju. Prema heteroanamnezi, saznajemo da je dječaka mjesec dana prije hospitalizacije ogrebala mačka. Potom su se razvili simptomi u vidu glavobolje i mučnine uz povišenu tjelesnu temperaturu i uvećane periferne limfne čvorove. Po prijemu realiziraju se laboratorijske i radiološke pretrage kao i hitni pregled očnog dna. Sve realizirane pretrage su bile uredne. U dva navrata urađena je lumbalna punkcija, hemizam i kulture likvora uredne. Tretman ovog kompleksnog slučaja uključivao je multidisciplinarni pristup od strane infektologa, tima intenzivne njege, neuropedijatra, imunologa, kardiologa, gastroenterologa i radiologa. Odluči se za konzervativni pristup, te započne antibiotska i simptomatska terapija uz monitoring. Četvrti dan hospitalizacije učini se ekstubacija, te se kontinuirano prate vitalni parametri, koji su stabilni. U dogovoru sa neuropedijatrima, devetog dana hospitalizacije, pacijent se premješta na Odjel neuropedijatrije radi dalje dijagnostičke obrade i liječenja. Zaključak: ovaj prikaz slučaja naglašava važnost razmatranja bartoneloza kao potencijalnog uzroka neuroloških simptoma i ispada. Ključni faktori za poboljšanje ishoda pacijenata sa encefalopatijom su rano prepoznavanje uzroka i pravovremeno liječenje, kao i multidisciplinarni pristup radi kompleksnosti dijagnoze.

Ključne riječi: encefalopatija, Bartonella henselae, status epilepticus, bartoneloza, bolest mačijeg ogreba

INTRODUCTION

Encephalopathy is a term that refers to qualitative and quantitative disorders of consciousness due to brain tissue dysfunction. Various consciousness disorders can be associated with motor dysfunction (pyramidal or extrapyramidal origin), epileptic seizures, symptoms and signs of increased intracranial pressure and damage to higher brain functions or mental regression, behavioral and sleep disorders, and psychiatric disorders. It can be caused by a generalized or focal brain tissue lesion. Based on the duration of disease, encephalopathies can be acute or chronic. Based on disease development, they can be progressive or non-progressive. They can be caused by various factors, either hereditary or acquired. Acquired acute encephalopathies can occur due to infection (encephalitis), disorders of circulation and tissue supply with oxygen (hypoxia and ischemia), as part of intoxications, after trauma and metabolic disorders (1).

Bartonellosis is a term used to describe infectious diseases caused by strains of Bartonella henselae. Bartonelloses of medical importance include Carrión's disease, trench fever, cat-scratch disease, bacillary angiomatosis and peliosis hepatis (2).

Cat-scratch disease, bacillary angiomatosis and peliosis hepatis are increasingly recognized as causes of disease in humans, particularly in immunocompromised groups such as HIV-infected individuals. Carrier animals serve as reservoirs for several zoonotic species of Bartonella. Chronic recurrent bacteremia is common in infected cats and likely facilitates vector transmission (3).

Cat-scratch disease is a common manifestation of B. henselae infection that usually presents with painful lymphadenopathy. Cat fleas are responsible for horizontal transmission of the disease (from cat to cat), occasionally arthropod vectors (fleas or ticks) can transmit the disease to humans (4). An infected cat is prone to chronic relapsing bacteremia which facilitates vector-borne transmission through a bite or scratch.

Cat-scratch disease is most commonly found in the pediatric population. In addition to lymphadenopathy, the disease manifests with fever, headache, loss of appetite and weight loss. Most cases show a self-limiting course of disease and do not require antibiotic treatment. More severe manifestations, such as Parinaud's oculoglandular disease, meningoencephalitis, hepatosplenomegaly and encephalopathy, occur in about 10% of patients (5,6).

The diagnosis is most often given based on a patient's history of contact with cats and a serological test showing a high level of IgG antibodies to B. henselae.

AIM

The aim of this case report was to highlight the potential neurological consequences that can arise as a complication of cat-scratch disease and to emphasize a multidisciplinary approach that is vital for a favorable prognosis. It is necessary to consider Bartonella henselae infection early in patients presenting with neurological symptoms who have previously reported symptoms typical of this infectious disease.

CASE REPORT

A six-year-old boy was brought to a medical facility unconscious, unresponsive, with dilated pupils, in a convulsive state with twitching of the extremities, a clenched jaw, and poor vital signs (SpO2 70%, HR 150/min). He was given Diazepam with direct oxygen support and transported to Clinical Center of Sarajevo. Atropine was administrated during the transport, Diazepam was repeated, along with Phenobarbitone. He was hospitalized at the Pediatric Clinic with a diagnosis of status epilepticus in the Pediatric Intensive Care Unit. Upon admission, the patient was comatose, with unstable vital signs, and placed on mechanical ventilation.

Medical history revealed that the symptoms began over a month ago. The patient had been scratched on his right arm by a cat. There was an ulcer-like lesion at the site, which was reddish and occasionally exuded pus. Subsequently, the parents noticed a swelling under the right armpit, approximately the size of an egg, hard and painful to the touch. He had difficulty moving his right arm. The child had a fever for four days, followed by the onset of headaches, weakness and nausea. His pediatrician prescribed a 6-day course of Azithromycin syrup, which led to a reduction in the axillary swelling, though the headaches persisted every day. On the day of admission, the mother reported that the patient had increasing difficulty rising from bed and experienced weakness in his lower limbs. A convulsion occurred suddenly, characterized by body rigidity with gaze fixation, hypersalivation and central cyanosis. Upon admission, blood samples were taken for detailed microbiological and serological testing, as well as complete laboratory testing.

Laboratory results at admission: ABB: pCO2 16.26 kPa, pO2 14.9 kPa, HCO3 18.2 mmol/L, BE -7.7 mmol/L, Complete blood work: Leukocytes 24.7 x109/L, Erythrocytes 4.94 x1012/L, Haemoglobin 124 g/L, Haematocrit 0.39 %, MCV 79 fL, Platelets 373 x109/L, Differential blood count (%): Neuthrophils 93.5 %, Lymphocytes 4.7 %, Monocytes 1.6 %, Eosinophils 0.2 %, Basophils 0.0 %. Coagulation: fibrinogen 2.4 g/L, INR 0.93, D-dimer 0.84 ng/mL, APTT 31.7 sec. Blood glucose 11.9 mmol/L, urea 2.2 mmol/L, creatinine 26 µmol/L, AST 32 U/L, ALT 15 U/L, GGT 10 U/L, Calcium 2.22 mmol/L, Sodium 137 mmol/L, Potassium 4.7 mmol/L, Chlorides 102 mmol/L, LDH 368 U/L, CRP 5 mg/L, CK 68 U/L, ALP 127 IU/L, Albumins 42g/L, globulins 31g/L, bilirubin 5.3µmol/L. CSF chemistry: Glucose 5.8 mg/dl, chlorides 120 mmol/L, protein 0.4 mg/dl, Le 0 cells/µL Er 0 cells/µL, lactates 2.3mmol/L. Urine: clear, yellow, glucose positive, Erythrocytes 3-4, nitrites negative, Leukocytes 6-8, some bacteria.

Midazolam was administered continuously. Fundus exam was clear. An infectious disease specialist was consulted, Trimethoprim-sulfamethoxazole, Rifampin, Vancomycin, Ceftriaxone, Acyclovir were administered. B. Henselae infection was suspected. Head CT and MRI were normal, except for shadowing in the sphenoidal sinus, most likely due to acute inflammatory changes. The neuropediatrician prescribed Phenobarbitone. Following consultation with both the infectious disease specialists and the neuropediatrician, a lumbar puncture was performed. PCR CNS multiplex was negative, the autoimmune encephalitis panel was clear, serologies for HSV, CMV, West Nile virus, Borrelia burgdorferi were negative.

On the fifth day of hospitalization, the patient was extubated, conscious, communicative, with normal vital signs. The child was then transferred to the Neuropediatrics department for further diagnostic evaluation and treatment. No further convulsions were noted during the stay. Standard EEG registration was normal. The patient was under continuous multidisciplinary monitoring by a neuropediatrician, immunologist, cardiologist, ophthalmologist, otorhinolaryngologist, maxillofacial surgeon and infectious disease specialist. Therapy for suspected Bartonella henselae infection was discontinued on the twenty-first day, based on recommendation of the infectious disease specialist. During the rest of his stay at the clinic, the patient remained conscious, afebrile, with normal vital signs, normotensive, regular diuresis and bowel movements. From the twentieth day of hospitalization, a mild hand tremor was observed, which significantly improved by the time of discharge. After discharge, a serology report for Bartonella henselae was recieved: IgM Monotest Bartonella henselae - negative, IgG Monotest Bartonella henselae - positive 1.472.

Four days after discharge, the patient presented to his primary care physician with complaints of tremors and low-grade fever. In the early morning hours, the patient experienced a generalized convulsive episode, which was treated with a Diazepam enema, followed by intravenous Diazepam. Subsequently, two more seizures occured, which resolved spontaneously. When the next convulsion occured, Phenobarbitone was administered. However, the seizure did not resolve, and the patient entered status epilepticus, which lasted for 20 minutes. After that, the boy responded only to painful stimuli, with non-reactive pupils. The patient was intubated and transferred to the ICU. On admission to the ICU, the patient was not breathing spontaneously, and was placed on mechanical ventilation (pulse 114/min, SpO2 100%, BP 120/72 mHg).

Laboratory findings on admission: SE 2 mm/h, CRP <5 mg/L, Leukocytes 7.3x109/L, Erythrocytes 4.3x1012/L, Haemoglobine 107 g/L, Haematocrit 0.32 %, Platelets 190x109/L , fibrinogen 1.9 g/L, INR 0.97, D dimer 0.36 ng/ml, APTT 30.7 sec, blood glucose 11 mmol/L, urea 2.9 mmol/L , creatinine 2.35 µmol/L , AST 23 U/L, ALT 17 U/L, GGT 51 U/L, ionogram normal, blood culture sterile.

A pulmonologist, neuropediatrician and psychologist were consulted. An MRI of the cranium and cervical spine was performed, which was normal. An EEG was also conducted.

Antiepileptic therapy was initiated and a diagnosis of epilepsy was made. The patient did not experience any more seizures during hospitalization, though the tremor remained present.

DISCUSSION

Neurological manifestations of cat-scratch disease are rare but can be very serious. This case report describes encephalopathy associated with B.henselae infection in a pediatric population, including the clinical presentation, diagnostic workup, treatment and outcome. It highlights the severe neurological manifestations of cat-scratch disease, such as altered consciousness and status epilepticus. Other authors have reported similar symptoms in their case reports and studies.

There are very few studies addressing the prevalence of neurological symptoms in cat-scratch disease. Existing literature has indicated that only 0.17-2% of all cases of cat-scratch disease develop encephalopathy (7,8).

Carithers HA, et al., (1991) published a study on the clinical presentation of cat-scratch disease, which included 76 patients. The average age of onset of encephalopathy was 10.6 years, almost twice more frequent in males than in females. Convulsions were reported in 46% of the patients. Laboratory diagnostics, as well as neuroradiological findings, were unremarkable. 78% of patients recovered within 1-12 weeks. There were no neurological sequelae (9).

Armengol CE, et al., (1999) published a study in which status epilepticus and encephalopathy caused by cat-scratch disease were described in six school-aged patients. The causative agent (B.henselae) was isolated via ELISA testing (10).

Cherinet Y, et al., (2008) also published a case report describing acute encephalopathy in a 9-year-old boy with partial convulsive seizures, where B.henselae was identified as the causative agent. A month after recovery, a repeated convulsive attack occurred, after which carbamazepine was prescribed. Six months after discontinuing the therapy, the patient developed a deja vu phenomenon with EEG abnormalities (7).

Smith RA, et al., (2007) described a case of a 7-year-old boy with acute encephalopathy and retinitis. Symptoms began two weeks prior with fatigue and lymphadenopathy, followed by fever, headache and vomiting. Serologically proven cause was B.henselae. The patient fully recovered (11).

CONCLUSION

This case report hightlights the importance of obtaining a detailed patient history and considering infectious diseases in patients presenting with neurological symptoms. It is important to consider Bartonella henselae infection in all patients with prolonged fever and painful lymphadenopathy, particulary in children. In cases with severe presentations and neurological symptoms, a multidisciplinary approach is imperative to ensure timely diagnosis and treatment, thereby improving the patient's prognosis.

ABBREVIATIONS

B. hensellae-Bartonella henselae
IgG-immunoglobulin G
IgM-immunoglobulin M
ABB-Acid base balance
CT-Computed tomography
MRI-Magnetic resonance imaging
PCR-Polymerase chain reaction
HSV-Herpes simplex virus
CMV-Cytomegalovirus
ICU-Intensive Care Unit
BP-Blood pressure
MCV-Mean Corpuscular Volume
INR-International Normalized Ratio
APTT-Activated Partial Thromboplastin Time
AST- Aspartate aminotransferase
ALT-Alanine aminotransferase
GGT-Gamma-glutamyl transferase
LDH-Lactate dehydrogenase
CRP-C-reactive protein
CK-Creatine kinase
ALP-Alkaline Phosphatase
CSF- Cerebrospinal fluid
SE-Sedimentation rate
EEG-Electroencephalogram
ELISA-Enzyme-Linked Immunosorbent Assay

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Hepatocellular Carcinoma in a Patient with Liver Cirrhosis: Surgical Resection of a Tumor in the Second and Third Segments of the Liver

Hepatocelularni karcinom kod bolesnika sa cirozom jetre: hirurška resekcija tumora drugog i trećeg segmenta jetre

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ABSTRACT

Introduction: hepatocellular carcinoma (HCC) is the most common form of primary liver malignancy. It is frequently associated with liver diseases, such as cirrhosis, with risk factors including hepatitis B and C infections, alcoholism, and fatty liver disease. The diagnosis of hepatocellular carcinoma is established through a combination of clinical, radiological, and laboratory findings, with treatment options including surgical methods such as liver resection, radiofrequency ablation, or arterial embolization. Case report: this case involved a 62-year-old patient diagnosed with hepatocellular carcinoma in the second and third segments of the liver, who underwent surgical resection of these segments. The following text reviews the diagnostic procedures, therapeutic approach, and postoperative care provided to the patient.

Keywords: nepatocellular carcinoma, liver cirrhosis, liver resection, CT angiography, surgery, histopathological findings

SAŽETAK

Uvod: hepatocelularni karcinom (HCC) predstavlja najčešći oblik primarnog malignog tumora jetre. Često je povezan s bolestima jetre, poput ciroze, a rizični faktori uključuju infekcije hepatitisom B i C, alkoholizam te masnu bolest jetre. Dijagnoza hepatocelularnog karcinoma temelji se na kombinaciji kliničkih, radioloških i laboratorijskih nalaza, dok liječenje može uključivati kirurške metode poput resekcije jetre, radiofrekventnu ablaciju ili embolizaciju arterije. Prikaz slučaja: ovaj slučaj prikazuje 62-godišnjeg pacijenta s dijagnozom hepatocelularnog karcinoma u drugom i trećem segmentu jetre, kojem je izveden kirurški zahvat resekcije tih segmenata jetre. U daljnjem tekstu razmatramo dijagnostičke postupke, terapijski pristup i postoperativnu njegu pacijenta.

Ključne riječi: hepatocelularni karcinom, ciroza jetre, resekcija jetre, CT angiografija, operacija, histopatološki nalaz

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary malignant liver tumor (1). Its occurrence is often associated with prior liver damage, typically in the form of cirrhosis, caused by hepatitis B and C infections, alcoholism, or fatty liver disease. Although early-stage HCC is frequently asymptomatic, disease progression may lead to nonspecific symptoms such as abdominal pain, weight loss, and jaundice (2).

Diagnostic methods primarily include ultrasound, CT, MRI, and specific biochemical markers, such as alpha-fetoprotein (AFP) (3). Treatment depends on the stage of the disease and the patient's overall condition and may involve surgical methods (liver resection, transplantation) or local therapies (radiofrequency ablation, embolization).

In this case, a patient with acquired liver cirrhosis and a diagnosis of hepatocellular carcinoma in the second and third liver segments underwent surgical resection (4).

This case report presents all diagnostic findings, procedures, and complications that arose during the treatment process.

CASE REPORT

A 62-year-old male patient was admitted to the Clinic of General and Abdominal Surgery diagnosed with hepatocellular carcinoma (HCC). His medical history includes long-standing hepatitis C infection, liver cirrhosis, and intermittently elevated alpha-fetoprotein (AFP) levels. Based on CT angiography and liver MRI, a lesion was detected in the second and third segments of the liver, corresponding to the characteristics of hepatocellular carcinoma. The clinical presentation included weakness, occasional pain in the right upper quadrant of the abdomen, and elevated biochemical markers.

Liver CT angiography performed on 3 November 2024, revealed cirrhotic changes in the liver parenchyma with a focal lesion in the second liver segment that met the criteria for hepatocellular carcinoma (LI-RADS 5). Additionally, a millimeter-sized hypodense area was noted in the seventh liver segment, which was difficult to differentiate from other lesions.AFP levels were significantly elevated (1748.00 ng/mL).

Based on these findings, a decision was made to proceed with surgical resection of the tumor-affected liver segments.

TherapeuticApproach

The patient underwent surgery on 5 November 2024. The preoperative process included thorough preparation, laboratory tests and cardiological monitoring. The surgery began with a median laparotomy incision. During intraoperative ultrasound, the tumor in the second and third liver segments was clearly identified, followed by resection of these segments. The tumor in the second segment measured 21x15x14 mm and was located 4 mm from the liver capsule and 12 mm from the resection margin, which allowed for safe resection margins. Intraoperative hemostasis was successfully achieved, and drainage was placed in the liver bed to prevent postoperative complications. Postoperatively, the patient was transferred to the intensive care unit for close monitoring of vital signs and management of potential complications.

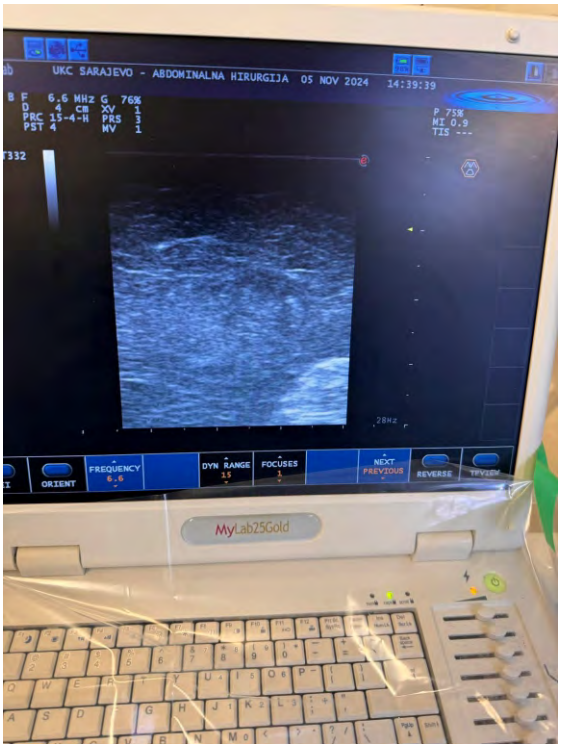

Figure 1 **Intraoperative ultrasound of hepatocellular carcinoma.**

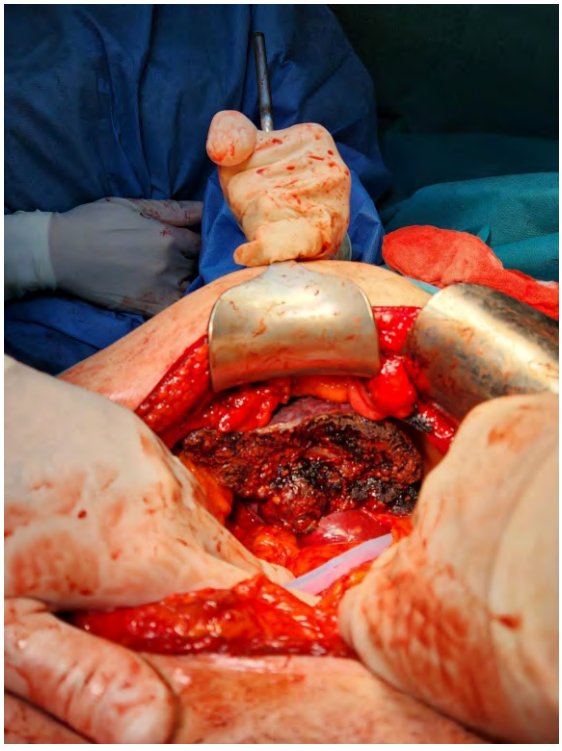

Figure 2 **Intraoperative look on liver.**

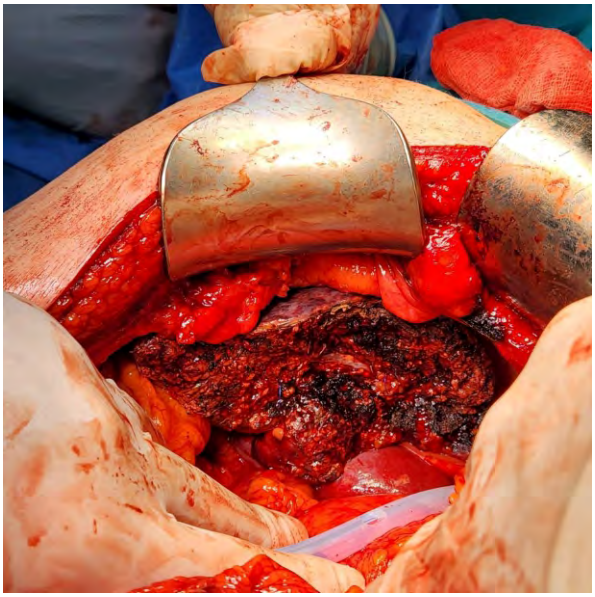

Figure 3 **Intraoperativ look on resected liver.**

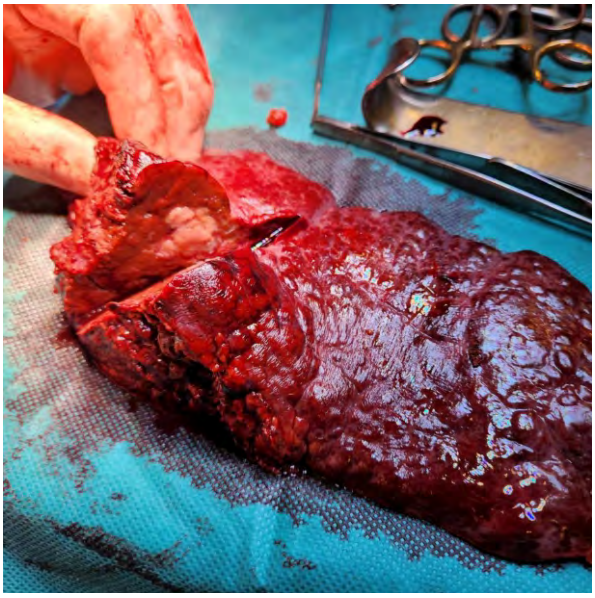

Figure 4 **Liver sample (section through carcinoma).**

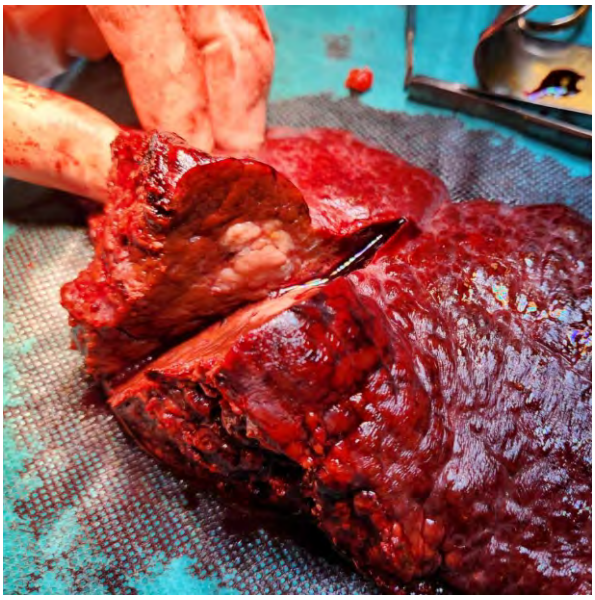

Figure 5 **Liver sample (HCC and cirrhosis hepatitis).**

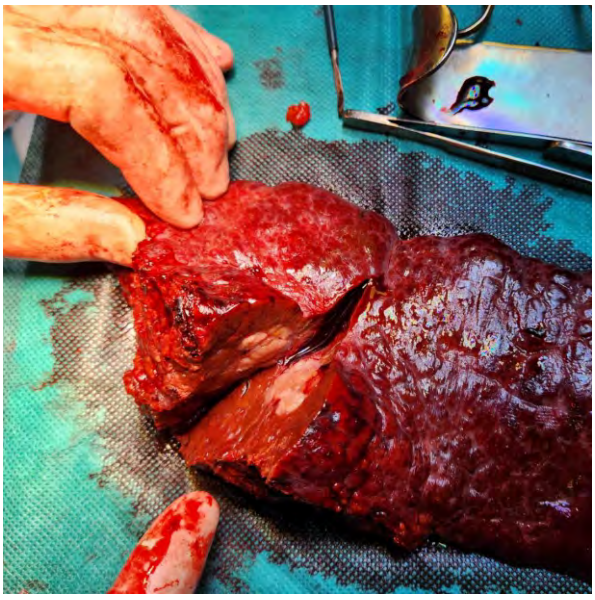

Figure 6 **Location of carcinoma (Seg II I III).**

Postoperative Course

The patient's postoperative condition was stable, with normalization of his vital signs. Laboratory results showed a mild increase in leukocytes (13.50 x10^9/L) and elevated bilirubin and liver enzyme levels, typical in the postoperative period for patients with liver cirrhosis. Platelet count was lower (128 x10^9/L), indicating thrombocytopenia in the context of cirrhosis.

With appropriate postoperative monitoring, the patient was successfully discharged after few days, with recommendations for continued oncological follow-up, including regular check-ups and ultrasound examinations to monitor for potential recurrences or metastases.

DISCUSSION

Hepatocellular carcinoma (HCC) remains a significant challenge in gastroenterology and surgery, particularly in patients with underlying liver cirrhosis.The diagnosis is based on a combination of radiological findings and histopathological criteria (5).

In this case, early detection of the lesion through CT angiography and MRI enabled the planning of an appropriate surgical intervention. With a multidisciplinary approach, the surgery was successfully performed, allowing the patient to achieve further disease control.

The treatment of hepatocellular carcinoma in the context of liver cirrhosis requires careful planning, as cirrhosis can complicate surgical interventions. Regular postoperative monitoring is crucial for detecting potential complications, recurrences, and metastases (6).

CONCLUSION

A multidisciplinary approach involving surgery, oncology, and radiology is essential to optimize treatment and improve the chances of long-term recovery for the patient. Further follow-up includes regular monitoring of alpha-fetoprotein levels, ultrasound, and CT/MRI examinations to detect any potential recurrences.

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A Rare Case of Potassium Permanganate Eye Chemical Injury

Rijedak slučaj hemijske povrede oka kalijum permanganatom

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ABSTRACT

Introduction: chemical injuries to the eye can vary in severity, with more severe cases resulting in significant consequences on ocular surface, patient's vision and overall life quality. Potassium permanganate, an alkali commonly used as a disinfectant, causes saponification of cell membranes facilitating the rapid penetration of substance through ocular structures, leading to severe tissue damage and visual impairment. Case report: this paper presents a case of a 74-year-old female who was admitted to our Clinic with a severe chemical injury of the right eye caused by an accidental contact with potassium permanganate powder. Following immense irrigation of the affected eye, biomicroscopic examination revealed extensive tissue imbibition with charcoal, black color disabling visualization of deeper structures. Visual acuity assessment indicated no light perception. A follow-up examination conducted three days later showed significant circular central epithelial corneal defect and stromal opacification, accompanied by a prominent avascular zone in the perilimbal region, without any visible tissue discoloration. Prompt and adequate acute management of the injury has resulted in enhancements in both visual acuity and the overall appearance of the ocular surface structures. Subsequent ophthalmological evaluations demonstrated continued improvement in corneal epithelium healing and stromal transparency, ultimately resulting in the complete restoration of the corneal epithelium and reduction in stromal opacification to discrete haze with the presence of several Descemet's folds. However, the size of the avascular perilimbal zone increased suggesting a possibility of poorer long-term prognosis. Regular follow-up appointments are essential to promptly identify and manage potential post injury complications. Conclusion: timely and appropriate management during the first few minutes and days following injury accompanied by advancements in ocular surface reconstruction techniques can immensely enhance long-term outcomes of severe chemical ocular injuries. Consequently, it is essential that the public, emergency medical teams and ophthalmologists are equipped to manage these patients effectively.

Keywords: chemical eye injury, potassium permanganate, perilimbal avascular zone

SAŽETAK

Uvod: hemijske povrede oka mogu imati različit stepen težine, a teži slučajevi rezultiraju značajnim posljedicama na površinu oka, vid pacijenta i ukupnu kvalitetu života. Kalijum permanganat, alkal koji se obično koristi kao dezinfekciono sredstvo, izaziva saponifikaciju ćelijskih membrana omogućavajući brzo prodiranje supstance kroz očne strukture, što dovodi do ozbiljnog oštećenja tkiva i samog vida. Prikaz slučaja: u ovom radu je prikazan slučaj 74-godišnje žene koja je primljena na našu Kliniku sa teškom hemijskom povredom desnog oka uzrokovanom slučajnim kontaktom sa prahom kalijum permanganata. Nakon izdašne irigacije zahvaćenog oka, biomikroskopski pregled je otkrio opsežnu imbibiciju tkiva ugljeno crnom bojom onemogućavajući prikaz dubljih struktura. Kontrolni pregled obavljen tri dana kasnije pokazao je veliki kružni centralni epitelni defekt rožnice i zamućenje strome, sa istaknutom avaskularnom zonom u perilimbalnom području, bez vidljive prebojenosti tkiva. Brz i adekvatan akutni tretman povrede rezultirao je poboljšanjem vidne oštrine i cjelokupnog izgleda površinskih struktura oka. Naknadni oftalmološki pregledi pokazali su napredak u cijeljenju epitela rožnice i prozirnosti strome, što je u konačnici dovelo do potpune obnove epitela i smanjenja opacifikacije strome do diskretne zamućenosti s prisutnošću nekoliko Descemetovih nabora. Međutim, povećala se veličina avaskularne perilimbalne zone što ukazuje na mogućnost lošije dugoročne prognoze. Redoviti kontrolni pregledi ključni su za promptno prepoznavanje i tretman mogućih komplikacija nastalih nakon povrede. Zaključak: pravovremeno i odgovarajuće liječenje tokom prvih nekoliko minuta i dana nakon povrede, praćeno inovacijama u operativnim tehnikama usmjerenim na rekonstrukciju površine oka, može značajno poboljšati dugoročne ishode teških hemijskih povreda oka. Shodno tome, neophodno je da javnost, timovi hitne medicinske pomoći i oftalmolozi budu optimalno opremljeni kako bi mogli pružiti efektivan medicinski tretman ovoj skupini pacijenata.

Ključne riječi: hemijska povreda oka, kalijum permanganat, perilimbalna avaskularna zona

INTRODUCTION

Severe ocular chemical burns constitute an ophthalmic emergency that necessitates immediate intervention. Such injuries can have a profoundly detrimental effect on a patient's vision and overall quality of life. Following an ocular burn, the progression of the condition occurs in several stages, each requiring timely and thorough management at each stage which is crucial for enhancing visual outcomes and minimizing the risk of complications (1).

Potassium permanganate ($KMnO_4$) is a potent alkaline and strong oxidative substance with disinfectant and astringent properties (2). As an over-the-counter preparation it is used for various dermatologic and vascular diseases, primarily in blistering, exudative conditions secondary to eczema, cellulitis and ulcers (3,4). For medical purposes, it is available in pre-made 0.01% solutions or in raw states as a crystal or granular powder that must be diluted to the aforementioned concentration for safe skin application (5).

CASE REPORT

We report a case of a 74-year-old female patient who was admitted to the Clinic of Eye Diseases of the Clinical Center University of Sarajevo as an emergency case due to a chemical burn of the right eye. According to the information provided by daughter, the patient who was living alone poured powder from a bottle containing potassium permanganate into her right eye instead of brimonidine tartarate solution (Bimanox). The patient used potassium permanganate on the recommendation of a dermatologist in a form of solution to treat exudative dermatitis with associated vasculitis on legs and arms.

Cataract surgery was performed in November 2022 and March 2023 on her right and left eye, respectively. Open angle glaucoma was diagnosed in 2023 after which the brimonidine tartrate solution was introduced as a regular antiglaucoma local therapy for both eyes.

The patient has a history of hypertension, atrial fibrillation and diabetes mellitus type II and is under treatment with antihypertensive medications, antiarrhythmics, direct oral anticoagulants (DOAC) and combined oral hypoglycemic medications and insulin. A heart pacemaker was implanted in 2019. Four weeks prior to hospitalization at our Clinic, the patient started using memantine hydrochloride and quetiapine as an addition to fluoxetine due to the progressive worsening of Alzheimer's disease symptomatology.

The best-uncorrected visual acuity (BCVA) of her right eye was no light perception (NLP) upon arrival. Prior to continuation of further ophthalmic examinations the right eye was copiously irrigated with sodium chloride 0.9% solution. The surrounding skin of the periorbital region was irritated and hyperemic. Biomicroscopic examination revealed an intense charcoal black, tar color of the entire anterior segment. There was a complete discoloration of the structures of the anterior segment, including not only the cornea and conjunctiva, but also the eye fornices, as well as the edges of the eyelids. Formed layer of color fused with the underlying tissue and could not be washed off or mechanically removed. Deeper structures could not be examined attributable to tissue imbibition with dye (Figure 1).

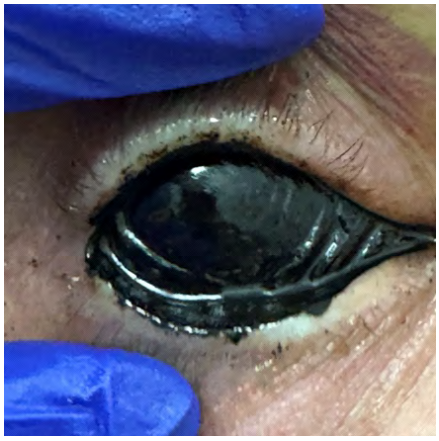

Figure 1 **Anterior eye segment completely discolored black at the moment of admission to the Clinic.**

After the biomicroscopic examination the speculum was placed on the patient's right eye (Figure 2) and the irrigation was continued during the next 12 hours through the intravenous giving set, confining the fluid delivery by using the tubing clamp to a drop-by-drop system.

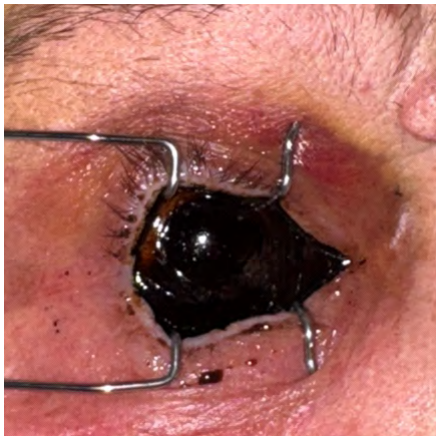

Figure 2 **Speculum placed on the injured eye after the initial irrigation.**

Over the next 12 hours, the eye was irrigated with a total of 1.5 liters of pure 0.9% sodium chloride solution and 1L of 0.9% sodium chloride solution mixed with an ampoule of vitamin C and gentamycin in a drop-by-drop system, along with generous eye washes with pure saline solution half-hourly (Figure 3).

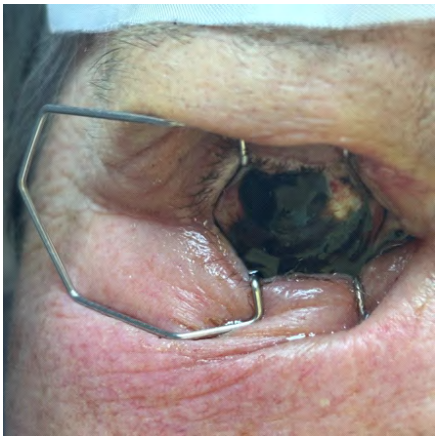

Figure 3 **Twelve hours post injury – eye irrigation confined to a drop-by-drop system with visible reduction in the anterior eye segment discoloration**

In addition to irrigation, local antibiotic therapy in the form of tobramycin eye drops (Tobrex), local antiglaucoma therapy with brimonidine tartrate (Bimanox) eye drops together with artificial tears was introduced.

First day of the admission to the hospital, removal of the remaining black potassium permanganate deposits from the conjunctiva and partially from the cornea was performed in the operating room under local anesthesia.

Biomicroscopic examination on the third day of hospitalization showed a hyperemic conjunctiva without black discoloration with slightly bare sclera at 7 o'clock and initial signs of symblepharon of the lower fornix. In perilimbal area there was a sectorial avascular zone from 6 to 10 o'clock. The cornea was keratopathic with a larger central circular defect of the epithelium and involvement of the stroma with an opaque, hazy central and more clear peripheral appearance. CA was formed, opalescent whilst deeper anterior segment structures were only partially visible (Figure 4). Visual acuity assessment exhibited hand movement (HM) vision.

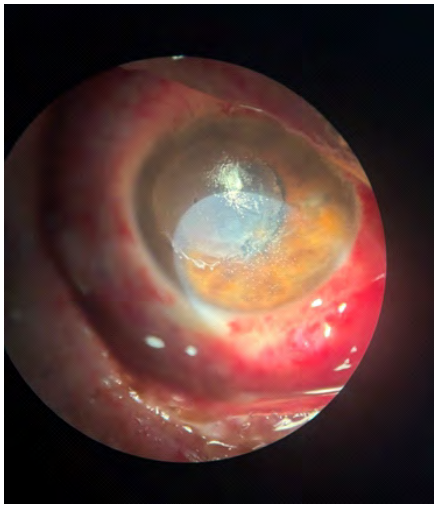

Figure 4 **Third day of hospitalization - sectorial avascular zone from 6 to 10 o'clock in perilimbal area, large central corneal epithelium defect and opacification of stromal tissue.**

Dexamethasone and gentamycin were applied subconjunctivally and continued until the end of hospitalization. Intravenous ceftriaxone (Triax) 2 grams BID was initiated for five following days alongside local application of autologous serum and atropine solution for the affected eye.

Two days later, a larger avascular zone was noted perilimbal in the range of 6 -13 o'clock. The cornea was clearer with marked signs of defect reepithelization, in a circular centripetal manner, prominently in the inferonasal corneal zone (Figure 5).

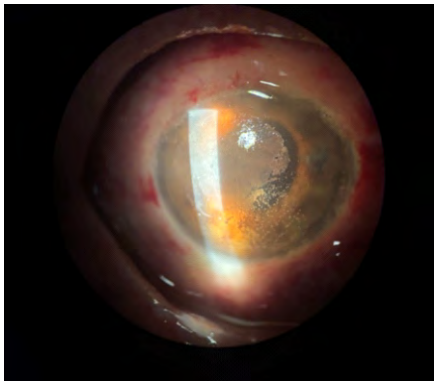

Figure 5 **Fifth day of hospitalization - sectorial perilimbal avascular zone in the range of 6 to 1 o'clock, cornea clearer with marked signs of defect reepithelization, dominantly in the inferonasal corneal zone.**

Tactile palpation of the right bulbus revealed slightly elevated intraocular pressure (IOP), estimated dig N+1. Hence, the local antiglaucoma therapy was changed and instead of brimonidine tartrate, combination of brinzolamide (Azopt) and timolol (Timalen) was commenced.

An ultrasound B scan of both eyes was performed showing changes in the vitreous typical of diabetic retinopathy with partial vitreous hemorrhage on both sides along with posterior vitreous detachment (PVD) on the left eye (Figure 6).

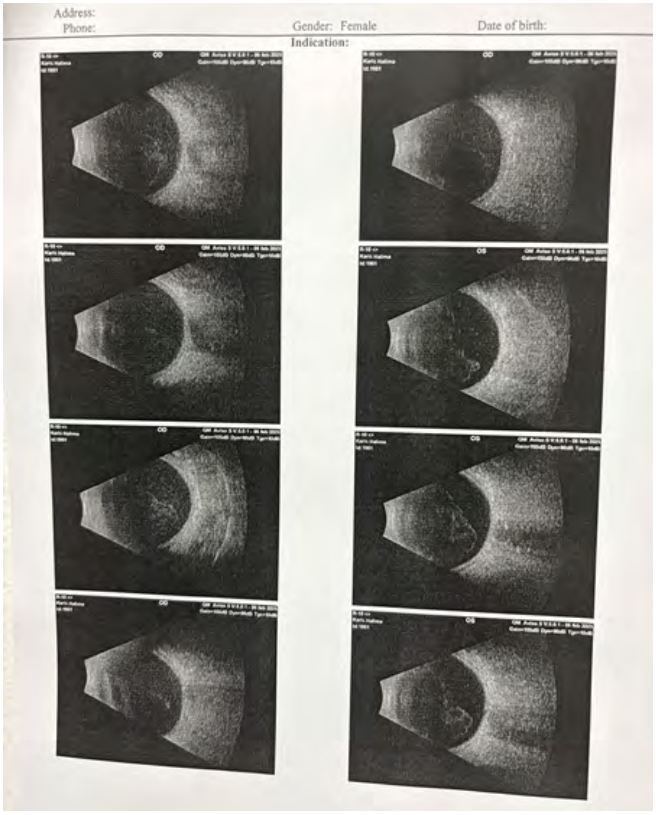

Figure 6 **B scan ultrasonography of both eyes - partial vitreous hemorrhage in both eyes alongside PVD in the left eye.**

On the twelfth day, perilimbal avascular was further enlarged to a zone from 6 to 2 o'clock. Corneal reepithelization of the central circular defect was continued centripetally revealing an overall enhancement in stromal transparency (Figure 7). Visual acuity was improved to counting fingers at about 10 cm. IOP estimated by digital palpation was normal. Patient was discharged with local antibiotic as well as antiglaucoma therapy and scheduled for a check-up.

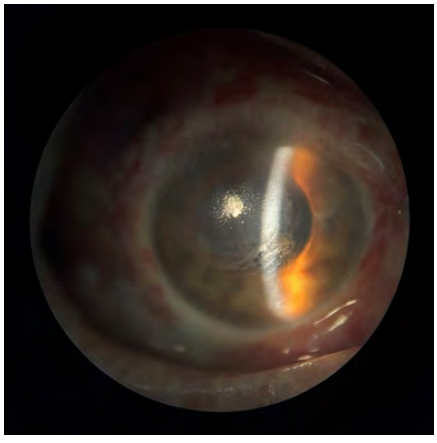

Figure 7 **Twelfth day of hospitalization - perilimbal avascular zone confined to a 6 to 2 o'clock range, continuation of corneal reepithelization with an overall enhancement in stromal transparency.**

A second check-up examination, two weeks after the hospital discharge, revealed complete restoration of central corneal epithelial defect as well as a significant reduction in stromal opacification to a mild haze with the presence of several Descemet's folds. Perilimbal avascular zone enlarged to a full 360° range (Figure 8). Visual acuity assessment indicated further advancement revealing acuity of counting fingers at about 100 cm. A local antiglaucoma therapy was discontinued as an IOP digital estimation displayed N-1 value.

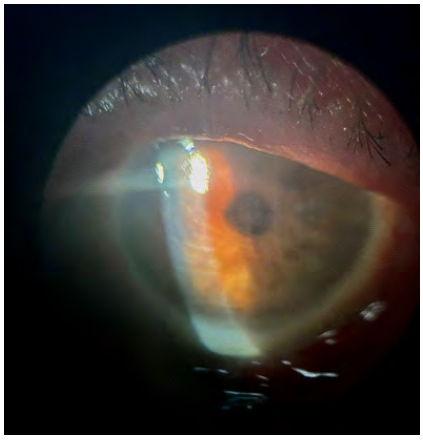

Figure 8 **Two weeks post discharge from the Clinic - complete restoration of central corneal epithelial defect, mild stromal haze with the presence of several Descemet's folds.**

A week later, third check-up examination was performed divulging a fluorescein staining confluent epithelial defect in the lower inferonasal paracentral corneal portion encompassed by a wider fluorescein stained girdle of perilimbal ischemic conjunctival and scleral tissue in the inferonasal portion (Figure 9).

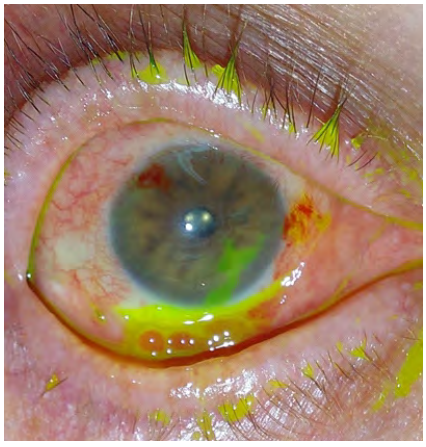

Figure 9 **Three weeks post discharge from the Clinic - a fluorescein stained corneal epithelial defects well as conjunctival and scleral ischaemia.**

Circumferential corneal neovascular pannus growing in from the perilimbal area could be visualised encompassing a zone from 10 to 2 o'clock (Figure 10).

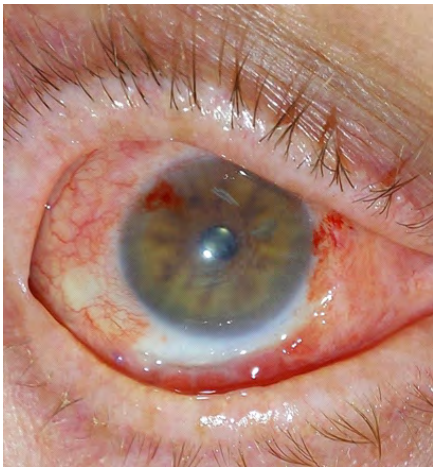

Figure 10 **Three weeks post discharge from the Clinic - perilimbal ischemia, 10 to 2 o'clock sectorial circumferential limbal neovascular pannus with mild central stromal opacification**

Visual acuity, as well as digitally measured IOP remained the same as on the previous check-up examination. Soft therapeutic contact lens was placed conjointly with intensification in local eye lubrication and continuation of previously introduced local antibiotic therapy.

DISCUSSION

Alkali agents account for approximately two thirds of chemical eye injuries (6).A critical factor influencing the toxicity of alkali is the pH level, where a pH greater than a 11.5 may lead to significant corneal damage (7). Alkali agents possess a higher penetration rate than acids (8).Among the common alkali substances leading to severe ocular burns, ammonia exhibits the fastest penetration rate (<3 minutes), followed by sodium hydroxide (3-5 minutes), potassium hydroxide (more than five minutes) and calcium hydroxide which shows variable penetration rate depending on crystallization (9). Potassium permanganate, a causative chemical compound in our case report, forms strong alkaline substance potassium hydroxide that causes protein denaturation and cytotoxic cellular damage with subsequent liquefactive necrosis allowing deep penetration into the tissues (10). In contrast, acid injuries tend lead to denaturation and coagulative necrosis of tissues that limits the penetration of acid into deeper structures (11).

For the effective treatment and prognosis, having a classification system for chemical eye burns is essential. Several such systems have been developed and are utilized in clinical practice. Two most frequently used classification systems are the Roper - Hall classification (Table 1) and Gupta D, et al. classification. In our case report, the Roper - Hall classification system was employed (12).The Roper – Hall classification is based on the extent of corneal injury and the presence of limbal conjunctival ischemia, a long - recognized key indicator of limbal stem cell damage, which significantly impacts recovery of the ocular surface (12,13). Based on the criteria established by Roper - Hall classification system, eye chemical injury presented in this report, caused by potassium permanganate was classified as a severe, grade 4 ocular chemical burn with potentially poor prognosis.

Table 1 **The Roper - Hall chemical eye injury classification system (Adapted from Roper-Hall MJ.Thermal and chemical burns. Trans Ophthalmol Soc UK (1962). 1965;85:631-53. PMID:5227208 (14)).**

Grade	Prognosis	Cornea	Limbus
I	Good	Damage of corneal epithelium	No limbal ischemia
II	Good	Corneal haze, iris details visible	<1/3 of limbal ischemia
III	Guarded	Total epithelial loss, stromal haze and iris details obscured	1/3 - 1/2 limbal ischemia
IV	Poor	Cornea opaque, iris and pupil obscured	> 1/2 limbal ischemia

A significant limitation of current classification systems is that, while they effectively grade the surface area of injury, they do not take into a consideration the depth of injury. In contemporary clinical practice, more accessible imaging modalities, such as anterior segment optical coherence tomography, may assist in documenting the extent of anterior segment structures involvement as well as wound healing to some degree (15,16).

The management of chemical eye injuries can be categorized based on 4 phases of healing: immediate, acute, early reparative and late reparative (1).

Decades of research underscore that the most critical intervention for chemical injuries remains prompt irrigation of the eye mitigating the severity of chemical burns and reducing the necessity for surgical interventions (17). Ideally, irrigation should occur before any comprehensive eye examination and should utilize isotonic saline or Ringer lactate solution, continuing until the pH normalizes to a physiological level (18). Topical anesthesia and speculum are imperative in assisting the irrigation procedure as it is recommended to administer at least 1 liter of fluid for duration of 30 minutes which may result in significant pain due to the denuded corneal epithelium (19). Care must be taken to cleanse the eye fornices from any residual material, as unremoved crystalline substances may lead to re-accumulation of alkaline chemicals post-irrigation (19).

Severe chemical injuries can result in significant inflammation. Hence, for decades topical corticosteroids have been a cornerstone of chemical injuries treatment owing to their role as anti-inflammatory agents that promote corneal reepithelization and stimulate stromal healing (20). Nonetheless, topical corticosteroids may inhibit healing of corneal wound that persists approximately one week post injury. Tapering the dose of topical corticosteroids after first 7-10 days post injury is recommended by a general consensus (18).

Reepithelization of the cornea presents a significant challenge in both acute and chronic management of chemical ocular burns. Chemical injuries can severely impair the function of goblet cells and Meibomian glands, leading to mucin and oil deficiencies in the tear film. Therefore preservative-free lubricants are essential for maintaining a moisturized ocular surface that facilitates corneal reepithelization and prevents further epithelial breakdown (21). Autologous peripheral blood serum (PBS) has been reported to accelerate epithelial healing in severe chemical injuries containing various growth factors, fibronectin, vitamins and other compounds proven to be crucial for corneal and conjunctival integrity (22,23).

In some scenarios, amniotic membrane transplantation (AMT) may be employed in acute ocular chemical burns to support reepithelization and reduce inflammation (24). For persistent corneal epithelial defects, several strategies such as punctal plug placement or soft contact lenses may assist in the healing process by minimizing ocular surface dryness and protecting the corneal surface from mechanical irritation by the eyelids, respectively (1).

Potent alkali agents can rapidly penetrate the anterior chamber, raising the pH of aqueous humor and inflicting severe damage to ciliary body which can cause hypotony and decreased ascorbic acid (ascorbate, vitamin C) secretion by the ciliary body (25,26). Ascorbic acid enhances the stemness of corneal epithelial progenitor cells and also accelerates corneal epithelial wound healing by promoting collagen synthesis in fibroblasts (27). Immediate treatment with ascorbate, whether topical or systemic, has been shown to reduce the risk of corneal ulceration and perforation (28).

Cycloplegic and mydriatic medications are utilized for pain relief in addition to iridocyclitis treatment and prevention or breakage of synechiae (18).

Severe chemical burns can lead to limbal stem deficiency which may necessitate in later stages either autologous or allogenic limbal stem cell transplants, derived from biopsy of limbal tissue or from culture expanded cells (29). In chronic management of chemical ocular burns, corneal transplantation may be considered. Penetrating keratoplasty (PKP) and deep anterior lamellar keratoplasty (DALK) can be performed in cases involving vision limiting corneal scarring (30), while Boston type-1 and osteo-donto keratoprosthesis (OOKP) remains the preferred treatment for the end-stage corneal disease not amenable to keratoplasty (31).

Chemical burns that compromise corneal architecture can distort the trabecular meshwork (TM), either by direct alkali substance action or by deposition of inflammatory cells in TM, leading to elevated IOP (32). Hence, there is a notably high incidence for glaucoma or worsening of preexisting glaucoma following severe ocular chemical injuries (32). Thereby, it is necessary to underscore the importance of regular IOP monitoring in these patients. Due to multifactorial etiology, increased IOP caused by chemical burns may display more resistance to conventional topical and systemic therapy (33). The cicatrization of conjunctival and underlying structures can lead to low success rates with trabeculectomy surgery, thus glaucoma tube surgery is more commonly performed, although it presents a challenge with significant revision rates (34). Cyclophotocoagulation may be effective for refractory post chemical burn glaucoma patients who display no response to previously mentioned treatment options (35).

CONCLUSION

Chemical eye burns are commonly encountered in emergency departments, often resulting from domestic accidents, workplace injuries or assaults. Potassium permanganate exhibits a potent caustic action when it comes in contact with the eye, leading to an extensive necrotic ocular tissue impairment. Key interventions for managing chemical eye injuries include reinforcing public health messaging on prevention and the urgency of immediate eye irrigation following eye chemical burn incidents as well as timely evaluation and treatment by an ophthalmologist. Intraocular pressure must be assessed and managed properly in the cases of severe eye chemical injury. In recent decades, advancements in ocular surface reconstruction techniques, such as stem cell treatment and keratoplasty have been milestones for better visual and prognostic outcomes in chronic course of the disease.

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Splenic Artery Aneurysm Rupture in Pregnancy

Ruptura aneurizme lijenalne arterije u trudnoći

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ABSTRACT

Introduction: rupture of a splenic artery aneurysm (SAA) during pregnancy is a rare but life-threatening condition with high maternal and foetal mortality. Due to its nonspecific clinical presentation, it is often misdiagnosed, leading to delays in treatment. Case report: we present the case of a 38-week pregnant woman (G1P0) who was admitted to the hospital in critical condition after repeated syncopal episodes. Foetal bradycardia was detected on ultrasound, necessitating an emergency caesarean section. Unfortunately, intrauterine foetal death had occurred, and massive intra-abdominal haemorrhage was observed intraoperatively. Due to postoperative deterioration, a re-laparotomy was performed, revealing a ruptured splenic artery aneurysm. A distal splenopancreatectomy was carried out. The postoperative course was complicated by pleural effusion and infection, but the patient eventually recovered successfully. Splenic artery aneurysms are the most common visceral arterial aneurysms, with an increased risk of rupture during pregnancy due to hormonal and hemodynamic changes. Early diagnosis and timely surgical intervention are crucial for survival. This case highlights the importance of considering SAA rupture in the differential diagnosis of acute abdominal pain and hemodynamic instability in pregnancy. Conclusion: although rare, splenic artery aneurysm rupture should always be considered in pregnant patients presenting with unexplained abdominal pain and shock. Timely diagnosis and aggressive surgical management are essential for improving maternal and foetal outcomes. Multidisciplinary collaboration between obstetricians, surgeons, and radiologists is a key to optimal patient care.

Keywords: splenic artery aneurysm, pregnancy, rupture, maternal mortality, emergency surgery, case report

SAŽETAK

Uvod: ruptura aneurizme lienalne arterije (ALA) u trudnoći rijetko je, ali životno ugrožavajuće stanje povezano s visokom smrtnošću majke i fetusa. Zbog nespecifične kliničke slike, često se pogrešno dijagnosticira, što dovodi do kašnjenja u liječenju. Prikaz slučaja: predstavljamo slučaj trudnice u 38. sedmici trudnoće (G1P0) koja je primljena u kritičnom stanju nakon ponovljenih epizoda sinkope. Na ultrazvuku je otkrivena fetalna bradikardija, što je zahtijevalo hitni carski rez. Tokom laparotomije uočeno je masivno intraabdominalno krvarenje, postoperativno pogoršanje stanja zahtijevalo je relaparotomiju, kojom je potvrđena ruptura aneurizme lienalne arterije. Urađena je distalna splenopankreatektomija. Postoperativni tok bio je kompliciran pleuralnim izljevom i infekcijom, ali se pacijentica uspješno oporavila. Aneurizme lienalne arterije najčešće su visceralne arterijske aneurizme, s povećanim rizikom rupture tokom trudnoće zbog hormonalnih i hemodinamskih promjena. Rana dijagnoza i pravovremena hirurška intervencija ključni su za preživljavanje. Ovaj slučaj naglašava važnost razmatranja rupture ALA u diferencijalnoj dijagnozi akutnog abdominalnog bola i hemodinamske nestabilnosti u trudnoći. Zaključak: iako rijetka, ruptura aneurizme lienalne arterije uvijek treba biti uzeta u obzir kod trudnica koje se prezentiraju neobjašnjivim abdominalnim bolom i šokom. Pravovremena dijagnoza i agresivan hirurški tretman od suštinskog su značaja za poboljšanje ishoda majke i fetusa. Multidisciplinarna saradnja između ginekologa, hirurga i radiologa ključna je za optimalno zbrinjavanje pacijentica.

Ključne riječi: aneurizma lienalne arterije, trudnoća, ruptura, smrtnost majke, hitna hirurgija, prikaz slučaja

INTRODUCTION

A splenic artery aneurysm is defined as a focal dilation of the splenic artery lumen that is at least 50% larger than its normal diameter (1). It is the third most common intra-abdominal aneurysm and the most frequent visceral artery aneurysm (60-70%) (2). Splenic artery aneurysms are rare but life-threatening, with an increased risk of rupture during pregnancy (3-4). The first successful treatment of a ruptured splenic artery aneurysm in pregnancy was described in the literature in 1940, while the first case of survival for both mother and foetus was reported only in 1967 (5-6). Given that these aneurysms are often asymptomatic, unruptured aneurysms are usually discovered incidentally during abdominal diagnostic imaging (native CT, CT angiography) (7). Rupture of a splenic artery aneurysm is rare, strongly associated with pregnancy, and most commonly occurs in the third trimester (8).

Although rare, ruptured splenic artery aneurysms should be considered in the differential diagnosis of acute conditions in pregnancy to improve treatment outcomes.

CASE REPORT

A 38-week pregnant patient (G1P0) was transported to the Obstetrics Department of the Clinic of Gynaecology and Obstetrics (GAK) of the Clinical Center University of Sarajevo (CCUS) by ambulance from the Institute for Emergency Medical Aid of Sarajevo Canton after she had reported to her gynaecologist's for CTG monitoring, where she collapsed three times. An emergency ultrasound revealed foetal bradycardia, prompting urgent referral to the GAK.

On admission, the patient was markedly pale, diaphoretic, and mildly somnolent while lying on a stretcher. Abdominal palpation revealed rigidity, but no vaginal bleeding was observed. Foetal heart activity could not be confirmed via CTG, and ultrasound examination verified the absence of a foetal heartbeat. The initial suspicion was placental abruption. Given the clinical findings and the critical condition of the patient, an emergency caesarean section was performed immediately.

A Pfannenstiel laparotomy was performed within five minutes of the patient's admission. Upon opening of the parietal peritoneum, fresh and clotted blood was found filling the abdominal cavity. A caesarean section was performed using the Dorffler method, delivering a stillborn infant.

Following this, the transverse incision was extended longitu dinally above the umbilicus. Aspiration and evacuation of blood and clots were performed. During abdominal exploration, a 3×3 cm hematoma was observed on the mesentery near the stomach on the left side, actively bleeding. The site was clamped and ligated. Exploration of the hepatosplenic spaces showed no additional bleeding. A nasogastric tube was inserted, revealing gastric contents without traces of blood. A full reassessment of the abdominal cavity and caesarean section site was performed, and a retro-uterine drain was placed in the pelvis.

Throughout the day, the patient remained stable, receiving three units of blood and three units of fresh frozen plasma of the matching blood type. Hemogram was done twice. Through the retro-uterine drain, a total of approximately 1500 mL of blood was collected.

Some 15 hours postoperatively, the patient experienced hypotension, tachycardia, and additional bleeding through the drain, of about 200 mL of blood. The patient reported abdominal pain. Due to hemogram decline and suspicion of active intra-abdominal bleeding, relaparotomy was indicated.

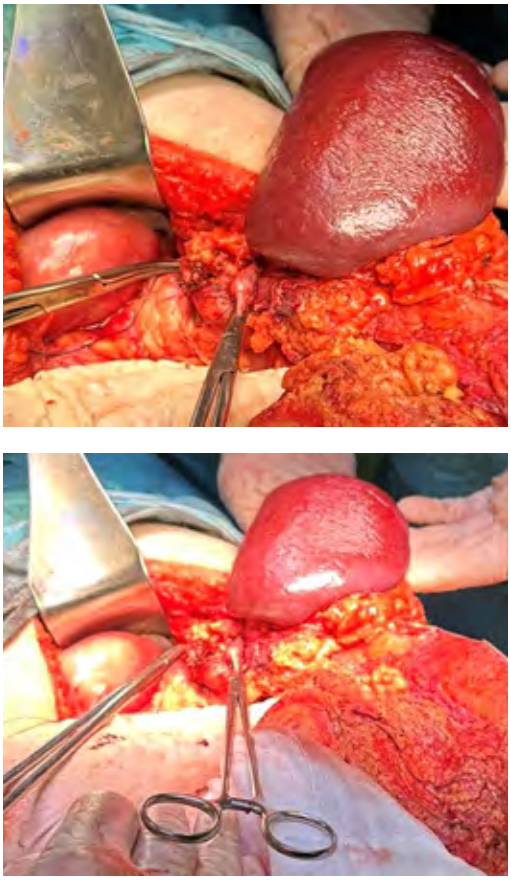

Figure 1 **Intraoperative picture of the ruptured splenic artery aneurism.**

An infraumbilical relaparotomy revealed a significant amount of both liquid and clotted blood. The uterus was found to be well-contracted, with a hemostatically intact incision. An abdominal surgeon was consulted and performed a supraumbilical relaparotomy with further exploration. Careful dissection led to the identification of a ruptured splenic artery aneurysm. A decision was made to perform a distal splenopancreatectomy, which was successfully executed.

Postoperatively, the patient remained hemodynamically stable and was closely monitored by a multidisciplinary team, including an abdominal surgeon, infectious disease specialist, cardiologist, pulmonologist, and haematologist.

During hospitalization at GAK, the patient received a total of 11 units of packed red blood cells and eight units of fresh frozen plasma of the matching blood type.

On the fifth postoperative day, she was transferred to the Clinic of General and Abdominal Surgery of the CCUS, where intravenous therapy (antibiotics, analgesics, anticoagulants, proton pump inhibitors, antiemetics, and crystalloid infusions) was continued. She was discharged in stable condition.

One day post-discharge, laboratory tests revealed elevated CRP (52mg/L) and anaemia with thrombocytosis. A follow-up abdominal surgeon consultation recommended evaluations by a haematologist and infectious disease specialist. The haematologist identified a heterozygous factor V mutation in the patient.

Eleven days post-discharge, the patient reported persistent cough, which lasted for ten days and pain under the left costal margin radiating to the back. Examination revealed tachycardia and reduced breath sounds on the left side. The pulmonologist suspected pleural effusion and referred her to the Emergency Medicine Clinic of the CCUS and to a thoracic surgeon. A diagnostic thoracocentesis was performed, draining 500 mL of serous fluid, with 40 mL sent for analysis. Chest CT confirmed left-sided pleural effusion. Bacteriological analysis identified Streptococcus viridans with broad antibiotic sensitivity. Biochemical and cytological tests indicated an inflammatory response.

Three days later, she returned to the pulmonary outpatient clinic with a fever of up to 39.5°C and an increased CRP (97mg/L). Antibiotics were prescribed. Despite treatment, pleural effusion recurred, and an additional thoracocentesis drained 900 mL of fluid. Inflammatory markers remained elevated, warranting hospitalization at the Clinic of Lung Diseases and Tuberculosis "Podhrastovi."

During hospitalization, another thoracocentesis yielded 500 mL of serous fluid, which tested sterile with no bacterial or inflammatory cellular elements. The patient showed progressive clinical improvement with antibiotic therapy, normalization of laboratory values, and radiographic resolution of pulmonary changes. She was discharged 13 days later in good condition.

Two months after hospitalization at the GAK, she underwent a follow-up gynaecological ultrasound, which was normal, and corresponds to the condition after a caesarean section.

DISCUSSION

A splenic artery aneurysm is the most common splanchnic artery aneurysm and ranks third in incidence among intra-abdominal aneurysms, following aortic and iliac artery aneurysms (9,10). The mortality rate of a ruptured aneurysm is 25%, but in pregnant women, it is disproportionately higher (75%), with a foetal mortality rate of up to 95% (8). Among all splenic artery aneurysms, 65% occur in pregnant women, and 50% of those rupture during pregnancy (11). The incidence of rupture during pregnancy is 12% in the first two trimesters, 69% in the third trimester (as in this case report), 13% during delivery, and 6% in the postpartum period (5,12-13).

The exact ethology remains unclear, with conflicting theories. Some authors believe that atherosclerosis and congenital arterial wall malformations are the primary causes, while others consider atherosclerosis to be a secondary factor (14,15). Another theory suggests that hypertension promotes aneurysm formation (16). Conditions associated with an increased incidence of splenic artery aneurysms include liver disease with splenomegaly, multiple pregnancies, systemic hypertension, and advanced age (15).

During pregnancy, the risk of rupture increases due to hormonal (oestrogen, progesterone, and relaxin) and mechanical changes (increased plasma volume and cardiac output, portal hypertension). Hormonal changes affect the arterial walls, leading to degeneration of the internal elastic lamina and fibrodysplasia. The resulting vascular wall weakening, combined with increased blood flow, can lead to aneurysm formation. Additionally, during pregnancy, the uterus compresses the aorta and iliac arteries, increasing splenic artery blood flow, which can cause aneurysm formation in a pre-weakened arterial wall. Since uterine diameter is largest in the third trimester, most ruptures occur during this period (11).

In patients with unruptured aneurysms, symptoms often include fatigue, vague abdominal pain, nausea, or vomiting. These nonspecific symptoms are commonly attributed to other conditions, leading to delayed diagnosis.

The most common symptom of rupture is severe, localized pain in the epigastrium or, more frequently, in the left upper quadrant, often radiating to the left shoulder (Kehr's sign). Additional symptoms include nausea, vomiting, and sudden collapse.

Signs of shock are a key indicator of rupture, though abdominal tenderness may also be present. In advanced pregnancy, an abnormal CTG recording may be noted.

Cases of ruptured splenic artery aneurysm have been described in the literature presenting similarly to pulmonary embolism, with symptoms such as left-sided chest pain, dyspnoea, low oxygen saturation, and ECG changes suggestive of massive pulmonary embolism (8). Ruptured splenic artery aneurysms are often misdiagnosed as uterine rupture or rupture of another arterial aneurysm, as they share many clinical features. Placental abruption is the most frequently misdiagnosed condition (17).

A "double rupture" phenomenon occurs in 25% of cases-initially, the bleeding is contained within the omental bursa for 6 to 96 hours, followed by free intraperitoneal haemorrhage and patient collapse (18).

A definitive diagnosis of splenic artery aneurysm rupture, particularly in emergency cases (as in this report), is often established during laparotomy, as urgent surgical intervention is required, leaving no time for extensive diagnostic evaluation.

In pregnant patients, ultrasound with pulsed Doppler is the preferred diagnostic method, although angiography remains the gold standard for diagnosing aneurysms. CT, MRI, and endoscopic ultrasound can also be used. X-ray may reveal an aneurysm if arterial calcification is present (19).

The management of a ruptured splenic artery aneurysm requires timely recognition and an aggressive surgical approach. The procedures described in the literature include: aneurysmectomy with splenectomy, distal pancreatectomy with splenectomy and ligation of the proximal and distal splenic artery, or isolated aneurysmectomy with splenic preservation (5). Splenic preservation is preferable but difficult to achieve in emergency settings where rupture has already occurred. Angiography and embolization have been successfully used for non-ruptured splenic artery aneurysms (20).

Timely diagnosis and successful treatment of a ruptured splenic artery aneurysm require a multidisciplinary approach, involving obstetricians, interventional radiologists, general or vascular surgeons, and anaesthesiologists.

CONCLUSION

Although rare, splenic artery aneurysm rupture should always be considered in the differential diagnosis of pregnant women with abdominal pain, especially those with signs of hemodynamic instability. Due to its rarity and similarity to other obstetric complications, splenic artery aneurysm rupture is often misdiagnosed during initial patient examination. Early diagnosis and proper management are key to reducing maternal and foetal mortality. The use of radiological examinations as a screening method is not a pragmatic approach due to the low prevalence of aneurysms in the general population.

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Toxic Hepatitis Caused by Dietary Supplements - Case Report

Toksični hepatitis uzrokovan upotrebom dodataka prehrani

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ABSTRACT

Toxic hepatitis is an inflammation of the liver that occurs in response to various substances, such as alcohol, drugs and various chemicals. It may develop either within hours or days, or after several months of exposure to a toxic agent. The most often signs and symptoms of toxic hepatitis include jaundice, itching, pain in the upper right abdomen, fatigue, loss of appetite, nausea and vomiting, rash, weight loss, and dark urine. One of the most important causes of liver dysfunction is drug-induced liver injury (DILI) which can lead to a wide spectrum of symptoms ranging from mild non-specific symptoms like asymptomatic transaminitis, acute hepatitis, chronic hepatitis, cholestasis to liver failure. The paper presents a case of a positive outcome of a 46 year old patient with toxic hepatitis who used a lot of different dietary supplements for several years with comorbidity of Gilbert syndrome and increased physical activity. The true incidence of DS (dietary supplements) induced liver injury (DSILI) is unknown but is probably under diagnosed due to the general belief of safety of these products. They are generally obtained without prescription and taken without specific medical advice or monitoring. In contrast to conventional drugs, however, the safety and efficacy of DS are not always well defined.

Keywords: toxic hepatitis, dietary supplements, liver injury

SAŽETAK

Toksični hepatitis je upala jetre koja nastaje kao odgovor na različite supstance, kao što su alkohol, droge i razne hemikalije. Može se razviti u roku od nekoliko sati ili dana, ili nakon nekoliko mjeseci usljed izlaganja toksičnom agensu. Najčešći znakovi i simptomi toksičnog hepatitisa uključuju žuticu, svrbež, bol u gornjem desnom dijelu trbuha, umor, gubitak apetita, mučninu i povraćanje, osip, gubitak težine i taman urin. Jedan od najvažnijih uzroka disfunkcije jetre je oštećenje jetre uzrokovano lijekovima (DILI) koje može dovesti do širokog spektra simptoma u rasponu od blagih nespecifičnih simptoma kao što su asimptomatski transaminitis, akutni hepatitis, hronični hepatitis, holestaza do zatajenja jetre. U radu je prikazan slučaj pozitivnog ishoda toksičnog hepatitisa kod 46-godišnjeg pacijenta koji je koristio veću količinu različitih suplemenata duž niz godina uz komorbiditet Gilbertovog sindroma i pojačanu fizičku aktivnost. Prava incidenca dodacima prehrani induciranog oštećenja jetre (DSILI) je nepoznata, ali je vjerojatno nedovoljno dijagnosticirana zbog općeg uvjerenja o sigurnosti ovih proizvoda. Dodaci prehrani se obično dobivaju bez recepta i uzimaju bez posebnog medicinskog savjeta ili nadzora. Za razliku od konvencionalnih lijekova, sigurnost i učinkovitost dodataka prehrani (DS) nisu još uvijek dobro definisane.

Ključne riječi: toksični hepatitis, dodaci prehrani, oštećenje jetre

INTRODUCTION

Toxic hepatitis is an inflammation of the liver that occurs in response to various substances, such as alcohol, drugs, and various chemicals. It can develop within hours or days, or after months or years of exposure to a toxic agent. Toxic hepatitis can permanently damage the liver, and in some cases, it can lead to liver failure. Mild forms of toxic hepatitis may be asymptomatic and are only detected by laboratory tests. The most common signs and symptoms of toxic hepatitis include jaundice, itching, pain in the upper right abdomen, fatigue, loss of appetite, nausea and vomiting, rash, weight loss, and dark urine (1,2).

Dietary supplements (DS) are consumed worldwide despite their unproven efficacy. The true incidence of DS-induced liver injury (DSILI) is unknown, but it is likely underdiagnosed due to the general belief in the safety of these products. Reported cases of liver injury caused by herbs and dietary supplements are increasing worldwide (3).

They are usually obtained without a prescription and are taken without specific medical advice or supervision. Unlike conventional medicines, the safety and efficacy of dietary supplements are not always well defined (4).

One of the most important causes of liver dysfunction is drug-induced liver injury (DILI), which can be categorized according to the clinical presentation into twelve "phenotypes". These phenotypes include: acute hepatic necrosis, acute (hepatocellular) hepatitis, cholestatic hepatitis, mixed hepatitis, elevated serum liver enzymes without jaundice, mild cholestasis, acute fatty liver with lactic acidosis, non-alcoholic fatty liver, chronic hepatitis, sinusoidal obstruction syndrome, nodular regenerative hyperplasia, and liver tumors such as hepatic adenoma and hepatocellular carcinoma (5).

Drug-induced liver injury (DILI) is a major health problem, and poses a challenge not only to healthcare professionals but also to the pharmaceutical industry and drug regulatory agencies (3).

Individual susceptibility to toxic liver damage is determined by a number of factors such as age, gender, genetic factors, pregnancy, nutritional status and possible associated diseases (5).

Toxic damage occurs either due to the direct toxic effect of a harmful agent, due to the formation of active toxic metabolites during degradation in the liver, or is a consequence of immune-mediated damage, whereby a drug or its metabolite becomes a hapten that turns certain cellular proteins into neoantigens (5,6).

In most cases, DILI is triggered by the bioactivation of drugs in a chemical way, whereby reactive metabolites have the ability to interact with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress. In addition, these reactive metabolites can disrupt ion gradients and intracellular calcium stores, resulting in mitochondrial dysfunction and loss of energy production. This impairment of cellular function can culminate in cell death and lead to liver failure (3).

There are two types of damage: predictable, caused by intrinsic hepatotoxic compounds, and unpredictable or idiosyncratic damage caused by idiosyncratic hepatotoxins (7).

Intrinsic DILI is most commonly caused by acetaminophen, and less commonly by aspirin, tetracycline, and vitamin A. Idiosyncratic DILI cases are caused by: Antibiotics (45.4%): amoxicillin-clavulanate (most common), sulfamethoxazole-trimethoprim, ciprofloxacin, isoniazid (INH); nonsteroidal anti-inflammatory drugs (NSAIDs), herbal and dietary supplements (HDS) (16.1%): green tea extract, anabolic steroids, multi-ingredient dietary supplements, cardiovascular drugs (10%): statins, amiodarone; central nervous system (CNS) agents: valproate, phenytoin; antineoplastic drugs: tyrosine kinase inhibitors, tumor necrosis factor inhibitors, alpha inhibitors, methotrexate (4,7,8,9,10).

Hepatocellular drug-induced injury is characterized by an ele vation of AST (aspartate aminotransferase and ALT (alanin aminotransverase) to at least twice the normal range and an ALT/ALP (alkaline phosphatase) ratio greater than 5. Cholestatic injury is characterized by an elevation of ALP to at least two times the normal range and an ALT/ALP ratio less than 2. There is also a mixed type of injury. Hypoalbuminemia is associated with salicylate toxicity. Lymphocytosis and eosinophilia are associated with immunological phenomena. Leukopenia and thrombocytopenia may reflect bone marrow suppression. Thrombocytopenia may indicate disseminated intravascular coagulation, which occurs with severe toxic hepatitis. Prolonged prothrombin time indicates severely impaired liver function and is an important prognostic sign. Amylase, CPK, and lactate may indicate muscle necrosis secondary to rhabdomyolysis (5). All patients with suspected DILI should undergo radiological evaluation, initially with abdominal ultrasound to assess for cirrhosis, biliary obstruction, or other focal liver lesions. Additional diagnostic tests, such as CT or MR cholangiography, may be used to evaluate for vascular abnormalities or pancreatobiliary disease (8). Liver biopsy is diagnostically useful to identify the type of liver injury and its severity (5). Biopsy may also be useful when liver biochemistry parameters or symptoms do not improve after drug withdrawal or the patient continues to have jaundice, and may be used to assess the severity of liver injury. General supportive care, including anti-emetics, analgesics, antipruritics, and parenteral hydration as needed, is recommended for all patients with acute DILI. Patients with severe nausea and vomiting, coagulopathy, altered mental status, or dehydration may require hospitalization for observation and monitoring (8,11).

AIM

The aim of the work was to draw attention to the occurrence of toxic liver damage caused by uncontrolled intake of herbal preparations and dietary supplements associated with excessive physical activity through a case report.

CASE REPORT

A patient born in 1979 was admitted to the Clinic of Gastroenterohepatology on 31 July 2024 due to extremely high transaminase values. Previously treated for 3 days at the Clinic of Heart Diseases, Blood Vessels and Rheumatism, where he was admitted through the Clinic of Emergency Medicine after a crisis of consciousness that occurred during a bicycle race. According to the patient, while riding a bicycle, he collapsed and fell off his bicycle. He did not remember the events of the last three minutes before the collapse. Subsequently, he woke up in the ambulance. There was no nausea or vomiting. He reconstructed the event in its entirety. Based on the examination by a neurologist (EEG and CT of the brain) and cardiologist (ECHO of the heart, 24-hour Holter ECG), cardiac disease was excluded. In the control findings at the Clinic of Heart Diseases, Blood Vessels and Rheumatism, a significant increase in transaminases was registered: AST 132 U/L...1597 U/L ....2210 U/L ALT 73 U/L....1998 U/L...5622 U/L LDH 302 U/L...2477 U/L...4933 U/L, slightly elevated bilirubin values: uk bilirubin 54.0 umol/L direct bilirubin 16.5 umol/l indirect bilirubin 37.5 umol/L, cardioenzymes CK 1385 U/L...1636 U/L....1350 U/L CKMB 147 U/L...238 U/L...190 U/L, with thrombocytopenia 124 x10^9/L....93x10^9/L. Hepatitis markers for B and C normal. A gastroenterologist was consulted who indicated urgent CT of abdomen and pelvis which showed liver of appropriate location, more voluminous, CC diameter of right lobe approx. 191 mm, homogeneous structure without clearly isolated focal changes. Contracted gallbladder of proper location. Intra and extrahepatic bile ducts were not dilated. Ductus choledochus was not conspicuous, portial vein as well as hepatic veins of appropriate diameters and opacification.

All branches of tr. coeliacus emerged directly from the aorta - anatomical variation. Accessory renal artery. Ectatic pyelons most likely in the area of atypical ureteral attachment. Other findings without particularities.

Previous diseases: Gilbert's syndrome diagnosed in 2009. Since 2011, he has been taking a large amount of supplements every day (Curcumin caps alternately,Whey protein 1x1 every day (from 25g to 50g per day), Creatine alternately (3g per day), Vitamin D 4000IJ in winter, 1000-2000IJ in summer, Glucosamine-chondroitin sulfate 1x1, Multivitamin 1x1, Omega 3 caps 1x1 every day, Magnesium 150-300mg per day. He occasionally consumes Forskolin,Tongkat ali, Beta alanine, BCAA (BRANCHED CHAIN AMINOACIDS), EAA (essential amino acids) and isotonic drink during longer training sessions. He was actively involved in sports (a combination of strength training and cycling). He did not smoke. He consumed alcohol (4-5 drinks per week). He had COVID-19 infection 2 on two occasions. Vaccinated against COVID-19 infection. He had Herpes zoster infection in 2022.

Physical examination on admission: conscious, oriented, communicative, afebrile, eupnoic at rest, medium osteomuscular structure and nutrition, mobile. Skin with a neat color. I do not palpate the enlarged PLZ.

Head and Neck: Head of normal configuration. Valle's points painless on palpation. Bulbs normoposed, neat convergences. Pupils circular, symmetrical, orderly reactions to light and accommodation. Sclera slightly icteric. Conjunctiva properly injected. The lips were pale, the mucous membrane of the oral cavity was moist, the tongue whitish. Pharynx and tonsils calmed. Teeth neat. Neck actively and passively movable in all directions.The thyroid gland was not palpable when enlarged. Chest: symmetrical, equally respiratory. Pulmo: percussively sonorous sound, auscultatory normal breath noise. Heart action rhythmic, tones clear, no murmurs heard TA 120/80 mmHg fr 60/min Abdomen: at the level of the chest, soft, painless on palpation, liver and spleen were not palpated enlarged. LL painfully insensitive to succession. Extremities: no edema. On the right knee and right elbow crusts and scratches. Pulse a. dorsalis pedis and a. tibialis posterior regularly palpable.

Laboratory findings at our clinic verified elevated ammonia 119 umol/L, total bilirubin 70.5 umol/L direct bilirubin 25.5 umol/L indirect bilirubin 45.0 umol/L AST 2748 U/L ALT 3258 U/L CK 456 U/L CKMB 70 U/L LDH 784 U/L GGT 123 U/L AP 88 U/L, INR 1.2, APTT 34.1 sec., D-dimer 2.3 mg/l, Tr 95 x10^9/L, normal proteinogram. Extended laboratory workup supplemented with screening for PAS (positive for Benzodiazepines), a panel of antibodies to autoimmune hepatitis and myositis in which a positive AMA-M2 was found. Serological diagnostics for TORCH infection normal. ABS findings normal. In the further course of treatment, there is a gradual decrease in the values of transaminases, bilirubin, normalization of ammonia values in the blood.

The patient was hospitalized at the Clinic of Gastroenterohepatology for 8 days, where he was treated with infusion solutions, hepatoprotectors, Ursodeoxycholic acid (UDCA), vitamin K, L-ornithine L-aspartate and Low molecular weight heparin (LMWH) only 3 days.The applied therapy resulted in an improvement of the patient's general condition with a moderate decrease in laboratory parameters based on reference values. Laboratory findings in the period of hospitalization to control findings are summarized in Table 1 - A clinical pharmacologist was consulted, who concluded that some of the supplements that the patient was taking, such as Curcumin and the herbal preparation Forskolin, might have a hepatotoxic effect, given that the patient was taking a large amount of supplements for more than 10 years, in combination with alcohol and a previous comorbidity of Gilbert's syndrome. All of the above, along with excessive physical activity accompanied by dehydration and exposure to high temperatures, might be a trigger for the development of acute liver failure.

The patient was discharged with recommendations for lifestyle changes, discontinuation of all nutritional supplements, strict abstinence from alcohol and continued hepatoprotective and UDCA therapy.

In the follow-up findings 3 months later, bilirubin 30.2 umol/L, ALT 91 U/L,AST, GGT,AP, LDH were within reference limits. Follow-up ultrasound of the abdomen, the liver was homogeneous, not enlarged, no focal lesions, SWE score of parenchymal fibrosis-F0. Pancreas echogenicity, regular shape and diagram, no focal lesions. The spleen was not enlarged, normoechoic.V. portae of appropriate diameter. No ascites.The patient subjectively felt well.

Table I **Laboratory results from the period of hospitalization to the control findings show gradual normalization towards reference values.**

Date	29.07.'24. [a]	31.07.'24.	01.08.'24.	05.08.'24. [b]	11.10.'24. [c]	Referance range
AST (U/L)	132	2210	2748	168	35	0-38
ALT (U/L)	73	5622	3258	1853	91	0-48
LDH (U/L)	302	4933	784	220	-	123-243
GGT (U/L)	-	-	123	118	40	11-55
AP (U/L)	-	-	88	88	80	46-116
Total bilirubin (umol/L)	54	-	70.5	33.7	30.2	1.7-20.5
Direct bilirubin (umol/L)	16.5	-	25.5	13.0	-	1.7-6.8
Indirect bilirubin (umol/L)	37.5	-	45.0	20.7	-	1.7-13.6
CKMMB (U/L)	147	190	70	49	-	<25
PLT	124 x10^9/L	93x10^9/L	95x10^9/L	119x10^9/L	148x10^9/L	150-400 x10^9/L
NH3 (umol/L)	-	-	119	54	-	18-72
APPT (sec)	-	-	34.1	29.0	-	25.9-36.6
INR	-	-	1.2	1.0	-	0.8-1.2

a On admission; b Discharge; c Control and follow- up

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; GGT: gamma glutamyl transpeptidase; AP: alkaline phosphatase; CKMB: creatine kinase myocardial band; PLT: platelets; NH3: ammonia; APTT: activated partial thromboplastin time; INR: international normalized ratio.

DISCUSSION

In most cases, drug-induced liver injury can cause mild to moderate elevations in liver function tests, but in rare cases it can be fatal. Many herbal remedies, dietary supplements, and other over-the-counter medications are often associated with liver injury, which can lead to complications, especially in patients with underlying liver disease. It is important to consult a primary care physician before starting any dietary supplement. The physician should review all medications the patient is taking and see if they interact with the supplements being considered. Drug-induced liver injury can be prevented by educating patients by clinicians about potential side effects after they start taking hepatotoxic medications. Clinical judgment by clinicians is required to balance the risks and benefits when patients start taking medications that may be hepatotoxic (6).

According to EASL guidelines, patients with DILI should undergo testing for hepatotropic viruses including hepatitis (A-E), particularly in those with acute hepatocellular injury. For completeness an autoantibody screen (antinuclear antibody, anti-smooth muscle antibody (ASMA)), M2-anti-mitochondrial antibody (AMA), liver microsomal antibody, immunoglobulins) should be undertaken. DILI assessment should also include coagulation profiles, as elevated prothrombin time ratio values may suggest impending acute liver failure (ALF) and prompt referral to a liver transplant unit should be considered. Abdominal ultrasound should be undertaken in all patients suspected of DILI to exclude any biliary, parenchymal or vasculopathy. Liver biopsy may be reasonable to consider in DILI, as histology may provide information pertaining to severity of liver injury and provide mechanistic insights by identifying specific patterns of injury. Liver biopsy is also warranted in those patients suspected of DILI when serology raises the possibility of autoimmune hepatitis. Liver biopsy may also be considered in patients whereby suspected DILI progresses, or fails to resolve on withdrawal of the causal agent, since histology may provide prognostic information assisting clinical decision particularly regarding immunosuppression (12).

Gilbert's syndrome is the most common inherited disorder of bilirubin glucuronidation and is the result of a mutation in the UGT1A1 gene, which results in reduced bilirubin activity by the uridine diphosphoglucuronyl transferase (UDPGT) enzyme. Patients with Gilbert's syndrome usually have mild and predominantly unconjugated hyperbilirubinemia without clinical significance. The diagnosis is based on higher values of unconjugated bilirubin in the blood without signs of liver pathology or increased breakdown of red blood cells (7). Plasma bilirubin concentration is usually below 50 umol/L with large inter-individual variations and with a tendency to increase bilirubin during stress: physical fatigue and exhaustion, infectious diseases, menstruation, hunger or alcohol consumption. Gilbert's syndrome is a benign disease that does not require therapy (5).

In the case of our patient, toxic liver damage was caused by dietary supplements used for many years without a doctor's recommendation, along with the comorbidity of Gilbert's syndrome and more frequent alcohol consumption, all accompanied by regular physical activity. Dehydration itself and exposure to high temperature in addition to the above led to a collapse and then a sudden increase in liver enzymes and ammonia. Based on the above, it could be conclude that it was a mild form of toxic hepatitis that was recognized in time and adequately treated. Abnormalities in laboratory findings and enlargement of the liver were recorded on the CT scan of the abdomen, without pronounced general symptoms during admission to our clinic. At follow-up examinations, the patient had no complaints with a further drop in liver enzymes according to reference values.

CONCLUSION

Toxic hepatitis (DILI) is clinically challenging to diagnose because it can mimic any acute or chronic hepatobiliary condition. The basic measure in treatment is to stop taking the hepatotoxic drug. Most patients recover well. In some cases, there may be a further worsening of the disease despite stopping the therapy. It is necessary to carry out a regular control examination of the liver status of the patient. Some forms of toxic liver damage are treated with adequate antidotes. In severe forms of toxic liver damage, the therapy is liver transplantation.

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Successful Treatment of Pulmonary Cystic Echinococcosis

Uspješno liječenje cistične ehinokokoze pluća

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ABSTRACT

Introduction: cystic echinococcosis has a worldwide distribution and is endemic in many regions where cattle are raised. Humans are accidental intermediate hosts. This parasitic disease most often affects the liver, then lungs and less often the other organs. Aim: we present a case of pulmonary cystic echinococcosis in a 33-year-old woman admitted to the University Clinic of Lung Diseases Sarajevo due to a chest CT scan verified infiltration in the left upper lung lobe. Case report: the patient reported a cough that had lasted for the past two months, with green sputum until five days before admission, when the sputum became extremely abundant, transparent, with a salty taste. She declared she had had surgery for a cyst in her left lung in childhood. Chest CT scan revealed a heterodense infiltration that is centrally cystic and peripherally soft tissue dense as well as multiple micronodules in the left upper lobe. In the serological ELISA test for Echinococcus granulosus IgG was positive. Bronchoscopic examination revealed only chronic bronchial inflammation. Albendazole therapy was started. Then a thoracotomy was performed with exploration of the pericyst and drainage of the left pleural cavum. Three months after the operation and albendazole treatment, chest CT scan showed a significant regression in the size of the left upper lobe infiltration. The team of thoracic surgeons made a decision on further monitoring of the patient. Conclusion: As our country is geographically located in an endemic region, echinococcal infection should be considered in the differential diagnosis of chest infiltrations.

Keywords: pulmonary cystic echinococcosis, diagnosis, treatment

SAŽETAK

Uvod: cistična ehinokokoza (CE) ima distribuciju širom svijeta i endemična je u mnogim regijama u kojima se praktikuje uzgoj stoke. Ljudi su slučajni posredni domaćini. Ova parazitarna bolest najčešće pogađa jetru, zatim pluća i rjeđe druge organe. Cilj: prikazujemo slučaj cistične ehinokokoze pluća kod 33-godišnje žene koja je primljena na Kliniku za plućne bolesti Sarajevo zbog CT-om prsnog koša potvrđene infiltracije u lijevom gornjem plućnom režnju. Prikaz slučaja: bolesnica je prijavila kašalj koji je trajao zadnja dva mjeseca, sa zelenim iskašljajem do pet dana prije prijema, kada je iskašljaj postao izrazito obilan, proziran, slankastog okusa. Izjavila je da je u djetinjstvu operirala cistu na lijevom plućnom krilu. CT prsnog koša otkrio je heterodenznu infiltraciju koja je centralno cistična, a periferno gustine mekog tkiva, kao i više mikronodula u lijevom gornjem režnju. U serološkom ELISA testu za Echinococcus granulosus IgG je bio pozitivan. Učinjena je bronhoskopija i ustanovljena je samo kronična upala bronha. Započeta je terapija albendazolom. Zatim je učinjena torakotomija s eksploracijom periciste i drenažom lijevog pleuralnog kavuma. Tri mjeseca nakon operacije i liječenja albendazolom, CT prsnog koša pokazao je značajnu regresiju veličine infiltracije lijevog gornjeg režnja. Tim torakalnih hirurga donio je odluku o daljnjem praćenju pacijentice. Zaključak: kako se naša zemlja geografski nalazi u endemskom području, u diferencijalnoj dijagnozi prsnih infiltracija treba uzeti u obzir ehinokoknu infekciju.

Ključne riječi: cistična ehinokokoza pluća, dijagnoza, liječenje

INTRODUCTION

Cystic echinococcosis (CE) is a neglected zoonosis caused by the larval form (metacestode or CE cyst) of the canine tapeworm cluster Echinococcus granulosus sensu lato (E. granulosus s.l.). Adults of this parasite inhabit the small intestine of dogs and other canids, while herbivores or omnivores serve as intermediate hosts in which the larval form develops after ingestion of parasite eggs that are released in the feces. Cystic echinococcosis has a worldwide distribution and is endemic in many regions where cattle are raised, including Mediterranean and Balkan countries. Humans are accidental intermediate hosts (1).

This relatively benign parasitic disease is characterized by slow-growing cysts most often in the liver (from 50% to 70% of cases), then in the lungs (20%-30%), and less often in the spleen, kidneys, heart, bones, central nervous system and other organs (2).

Hosts for the cestodes tapeworm may be subdivided into three categories: definitive, intermediate, and accidental. The definitive hosts are carnivores, notably dogs, cats, and wild canids, in which adult tapeworms (2.0–7.0 mm in length for Echinococcus granulosus and 1.2–4.5 mm for Echinococcus multilocularis) inhabit the small intestine. Domestic animals and other warm-blooded vertebrates, such as sheep, goats, cattle, horses, camels, and pigs, act as intermediate hosts, ingesting eggs released by carnivores, they carry Echinococcus granulosus predominantly. Humans may accidentally act as an intermediate host, although their role in the life cycle remains unclear (Figure 1) (3).

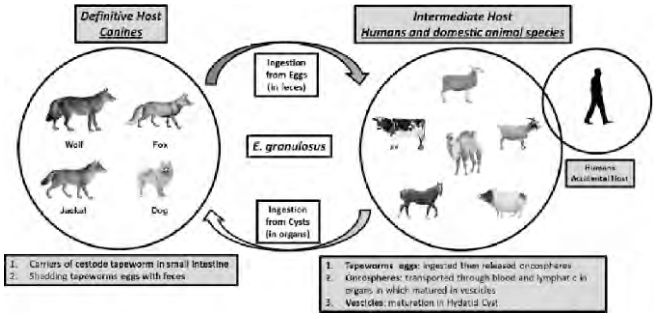

Figure 1 **Life cycle of Echinococcus granulosus between definitive, transitional and accidental host (3).**

CASE REPORT

We present a case of pulmonary cystic echinococcosis in a 33-year-old woman admitted to the Clinic of Lung Diseases and Tuberculosis of the Clinical Center University of Sarajevo due to the chest CT scan verified infiltration in the left upper lung lobe. The patient reported a cough which lasted for the past two months, with green sputum until five days before admission, when the sputum became extremely abundant, transparent, with a salty taste. On admission, she denied shortness of breath and chest pain and was not losing weight. On one occasion, she had an elevated temperature of up to 38°C. Appetite excellent. Stool and urination regular. Of the medicines, she took pholcodine hydrate caps 3x2 and levofloxacin tbl 500 mg 1x1.

Medical history

In her personal history, she declared she had undergone surgery due to a cyst in her left lung at the age of eight, and then was told that it was "cat hair". She had three hunting dogs at home now, properly vaccinated every year. No diseases related to heredity. Married, lived with her husband and two daughters. No food and drug allergies. Nonsmoker.

Upon admission in extremely good general condition, conscious, oriented, communicative, afebrile, eupnoic at rest, euhydric, independently mobile, of medium osteomuscular structure and nutrition. Cardiopulmonary compensated. Due to the suspicion of Echinococcus granulosus infection according to anamnestic data serology for Echinococcus granulosus and basic laboratory findings are immediately performed upon admission.

Basic laboratory findings

Leukocytes 13.90 x10^9/L (elevated), CRP 44.4 mg/L (elevated), IgE 224.00 g/ L (elevated). Erythrocytes, Hemoglobin, Hematocrit, MCV, MCH, MCHC, MPV, Platelets, INR, APTT, Sodium, Potassium, Calcium, Chlorides, Magnesium, Glucose, Urea, Creatinine, Total bilirubin, AST, ALT, CK, LDH and Alkaline phosphatase did not deviate from the reference values. In the serological ELISA test for Echinococcus granulosus IgG was positive - 25.5 U/ml.

Chest X-ray: Left hiloperihilar round spotty shadowing with pronounced bronchovascular pattern. Shaded left phrenicocostal sinus (Figure 2).

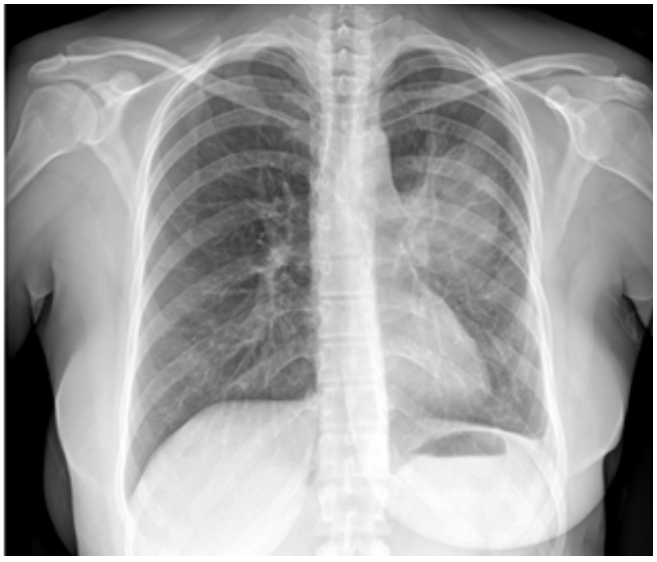

Figure 2 **Chest X-ray shows a mass in the hilar region.**

Chest CT scan with contrast medium was also performed (Figures 3 and 4). Chest CT scan revealed a heterodense infiltration that is centrally cystic and peripherally soft tissue dense in the left upper lobe, ventrally and with propagation into the mediastinum of open etiology: concerning the presence of a cystic component, it might be a large echinococcal lung cyst, less likely, but it also came into consideration that it was a cystic tumor process. The cystic component was about 60 mm in diameter. It infiltrates the segmental branches of the upper left lobar bronchus for the upper and lower lingular segments as well as for the anteromediobasal parts of the upper left lung lobe. A zone of atelectasis was visible distally. In the upper left lung lobe multiple micronodules were visible. No micro-nodular or nodular changes could be seen in the lower left and in all three lung lobes on the right. Enlarged lymph nodes with a diameter of up to 20 mm in the aortic window were visible in the mediastinum. Enlarged lymph nodes with a diameter of up to 16 mm were visible in the left hilus. No enlarged lymph nodes could be seen in the right hilus. On scans of the upper abdomen, signs of chronic calculous cholecystitis were isible. On scans with a bone window, signs of bone destruction were not observed.

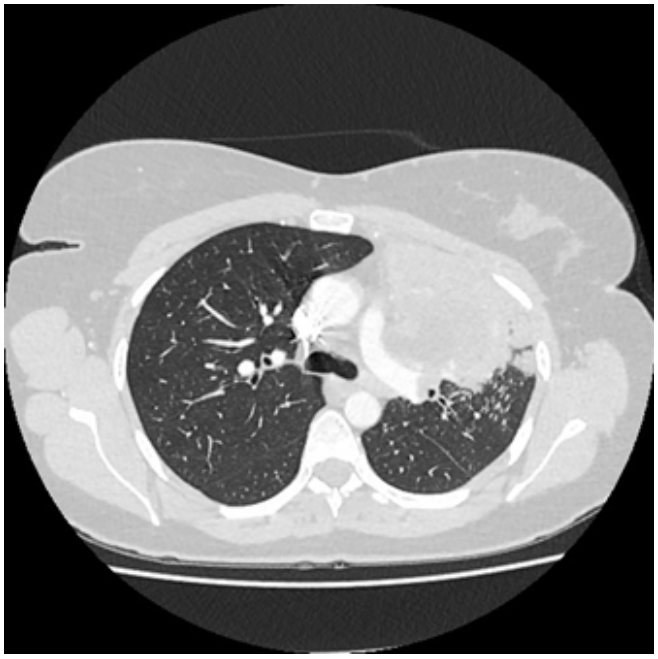

Figure 3 **Chest computed tomography shows the infiltration in the left upper lung lobe through the window for the lung parenchyma.**

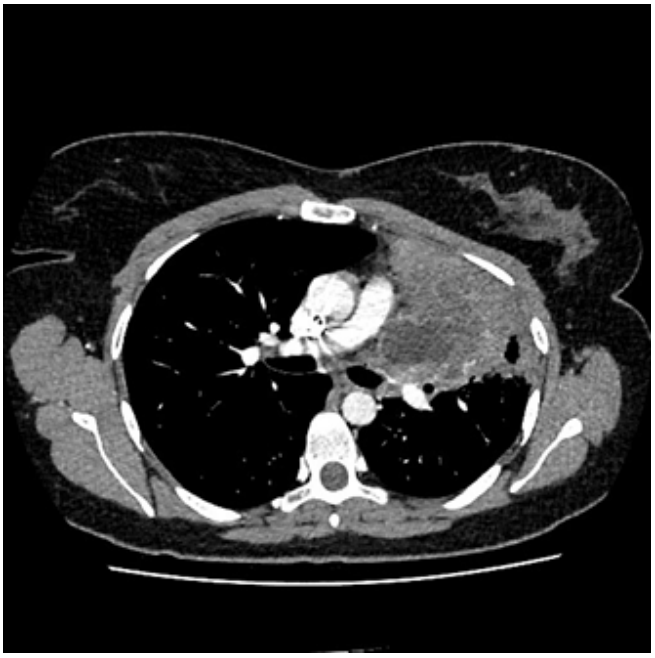

Figure 4 **Chest computed tomography shows the infiltration in the left upper lung lobe through the soft tissue window.**

Further diagnostic procedures

During hospitalization, one characteristic sputum described in the anamnesis was taken, but it arrived negative for scolex. In the further diagnostic process, an ultrasound of the abdomen was performed: Gallbladder with adequate wall thickness, intraluminally two choleliths up to 0.7cm in diameter. Intra- and extrahepatic bile ducts are not dilated. Bronchoscopic examination revealed only chronic bronchial inflammation.

Based on anamnestic data, clinical examination and diagnostic procedures, Echinococcus granulosus was suspected. After presentation at the Multidisciplinary Oncology Council, thoracic surgery was indicated. The treatment with anthelmintics, Albendazole 2x400 mg started; one cycle lasts 28 days, then a break of 14 days.Three cycles of therapy were planned.

The patient underwent a thoracotomy shortly after starting Albendazole therapy. Exploration of the pericyst, and drainage of the left pleural cavum were performed. The pathohistological finding of the ex tempore biopsy: In the examined frozen sections (two levels), a lung with signs of consolidation was seen with a rich predominantly chronic inflammatory infiltrate, which multifocally created lymphatic aggregates. In the examined sections the morphological picture suggested inflammatory changes. Subsequently, in permanent sections, the morphological picture remained the same, with a visible fragment of acellular lamellated material surrounded by foreign body-type multinucleated cells (possibly an endocyst fragment).

After three months, the chest X-ray (Fig. 5) and the follow-up chest CT scan (Fig. 6) were performed, and compared with the preoperative CT finding.

Comparison of postoperative chest CT scan with preoperative chest CT scan: Compared to the previous preoperative chest CT scan, the cystic component was in a good regression.The remaining infiltrate widely infiltrates the mediastinal pleura, was in intimate contact with the left contour of the trunk of the pulmonary artery and the left superior lobar pulmonary artery. Toward the periphery, the heterodense formation did not separate from the atelectatic parenchyma. The total dimensions of the remained infiltrate were 42x58x36 mm (they were about 74x75 mm in the preoperative chest CT scan). In the residual parenchyma of both left lobes, multiple infiltrations of predominantly fibrous and postoperative appearance were seen, partly in terms of atelectasis with a couple of micronodules. In the right lung, there was no zone of altered density of a nodular character.

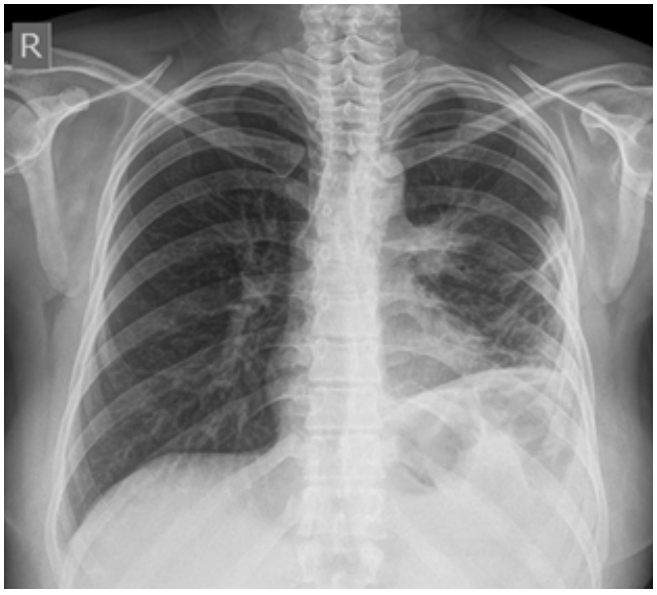

Figure 5 **Postoperative chest X-ray.**

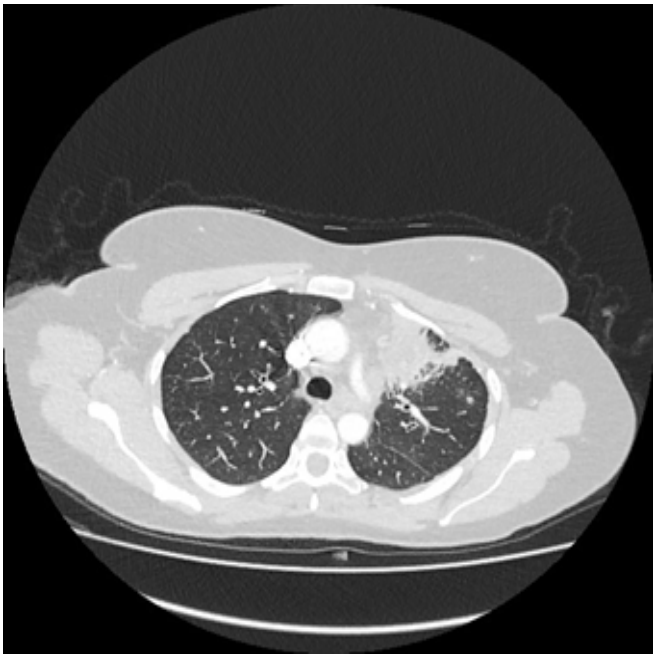

Figure 6 **Chest computed tomography through the soft tissue window shows a good regression of the cystic change in the left upper lung lobe.**

Chest CT scan was performed and radiological good regression was recorded. Further monitoring of the patient was indicated by the team of thoracic surgeons.

Chest CT scan performed another three months later showed left anterior and lateral postoperative scars. There were no signs of recurrence of the previously operated echinococcus. Mediastinal and hilar glands were not enlarged. The heart was retracted, pulled to the left. This chest CT showed significant regression compared to the chest CT done 3 months ago (Figures 7,8,9,10).

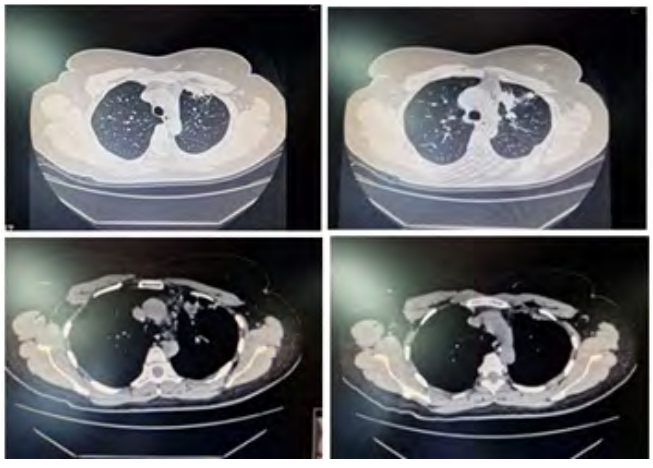

Figure 7, 8, 9, 10 **Significant regression on follow up chest CT three months later.**

DISCUSSION

Echinococcus granulosus can cause one or more hydatid cysts and most often affects the liver and lungs, and rarely the bones, kidneys, spleen and central nervous system. An infected person can live for years without symptoms during the incubation period until the cyst becomes large enough to cause symptoms. About 60% of people infected with Echinococcus spp. are without symptomatology (4).

The clinical manifestation of a pulmonary hydatid cyst depends on whether the cyst is normal or ruptured. Unruptured cysts have no special signs, and clinical manifestations depend on their location and size. Large cysts can cause compressive symptoms of adjacent organs and even superior vena cava syndrome (SVCS). The most common symptom in symptomatic patients is cough. Mediastinal cysts can damage adjacent structures, leading to bone pain, bleeding, or airflow limitation.

Cyst rupture can be accompanied by a sudden cough and fever. The entry of the contents of the cyst into the respiratory tract can be accompanied by the expectoration of a transparent liquid with a salty taste, which consists of a membrane and a scolex (5).

Primary diagnosis is made by chest X-ray, ultrasound and chest CT scan. In addition to routine tests, serological tests ELISA as a screening test and immunoelectrophoresis (IE) as a confirmatory test are available. The diagnosis is established if both ELISA and IE are positive. In this study, only ELISA for Echinococcus granulosus was performed, which could have been supplemented with an IE test, but the latter was not done for technical reasons. The cut-off values for ELISA in this University Clinical Centre are >15 U/ml and in the literature cut-off values for interpretation are: negative (<10 U/ml), indecisive (≥10 and <15 U/ml) and positive (≥15 U/ml) (6). Serology may be negative in 10-15% of cases, especially in well-encapsulated cysts. The sensitivity of serological tests for liver cysts is 80%-90%, and the specificity is 88%-96%. For lung cysts, the sensitivity is only 50%-60%. The IgG4 response is more pronounced than the IgG1 response (2). Also, IgE was 224.00 g/ L (elevated), which in the literature is highly parasite specific (7).

The primary treatment for pulmonary hydatid cyst is surgery. Intact cysts should be operated on immediately due to the risk of infection and rupture. Even if the parasite inside the cyst is dead, the remaining germinal membrane should be surgically removed, as it may be a source of infection. Today, in the operation of hydatid cysts, surgical methods are used to preserve as much of the lung parenchyma as possible (enucleation, cystotomy-captonage, pericystotomy and wedge resection). Resective surgery can be performed if more than 50% of the lobe is devastated (8).

Surgical treatment of cystic echinococcosis is contraindicated when there are multiple cysts, very small cysts, inactive cysts that are either calcified or difficult to access due to their localization, dead cysts, and if the patient's general condition does not allow it (9).

Although there are general recommendations on treatment, a final consensus on the approach to the disease has not been reached. The four treatment modalities currently in use are: 1) surgical treatment 2) PAIR (puncture, aspiration, injection of a protoscolicidal agent, reaspiration) 3) chemotherapy with albendazole or mebendazole 4) the so-called "watch and wait", a method of "monitoring and waiting" for inactive, clinically insignificant cysts. There is insufficient evidence to support any of these methods, in the sense that there are not enough clinical studies to guide clinicians, so the choice of therapeutic option for an individual patient remains controversial (9).

The team of our thoracic surgeons who treated our patient decided to perform a thoracotomy with pericyst exploration and drainage of the left pleural cavum. Before the surgery itself, Albendazole therapy was started and three cycles of therapy were planned, with a break of 14 days between cycles, and one cycle lasting 28 days. On the new chest CT scan performed 3 months after the operation of our patient, a good radiological regression in the left lung was recorded (the total dimensions of the formation are 42x58x36 mm, and they were previously about 74x75 mm).

The team of our thoracic surgeons decided for further patients monitoring (albendazol continued) and the next chest CT scan is planned in 3 months. Chest CT scan performed another three months later showed left anterior and lateral postoperative scars. There were no signs of recurrence of the previously operated pulmonary cystic echinococcus. In the paper by (7) a young woman with disseminated cystic echinococcosis was presented, in whom hydatid cysts were verified in liver, spleen, lungs, kidneys and pericardium. Due to the specificity of the form of the disease, the age of the patient and because of the frequent relapse of the disease after the end of therapy, was treated with albendazole for a long period of time (during 2 years she spent a total of 17 cycles of albendazole treatment through outpatient follow-up. Therapy was good all the time tolerated and there were no complications of treatment with antihelmintics). This group of authors presented a somewhat different mode of treatment for cystic echinococcosis, which resulted in favorable regression and control of the disease.

The guidelines on the modality and length of treatment vary, but generally there is a recommendation on prolonged treatment (9). Follow-up of the presented patient is ongoing. Prolonged treatment with albendazole in patients with disseminated cystic echinococcal disease evidently leads to a favorable effect in terms of subjective and objective improvement. The authors point out that the possibility of a toxic effect of the drug on the liver should not be a major concern with long-term treatment with albendazole (8).

CONCLUSION

It could be concluded that any radiologically verified infiltration in the chest requires a detailed anamnestic, clinical and diagnostic work-up. Since our country is geographically located in an endemic region, cystic echinococcal infection should be considered in the differential diagnosis of verified chest infiltrations. The selection of a therapeutic option for each patient is individual, a multidisciplinary team with a multimodal method of treatment should be involved in the diagnosis and treatment of cystic echinococcal infections in order to achieve the best result for the patient.

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