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Risk factor-based point-based scoring system - CHA_2DS_2 -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

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Major risk factors
Previous stroke
TIA or systemic embolism
Age ≥75 years

Clinically relevant non-major risk factors
CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%]
Hypertension
Diabetes mellitus
Age 65-74 years
Female sex
Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

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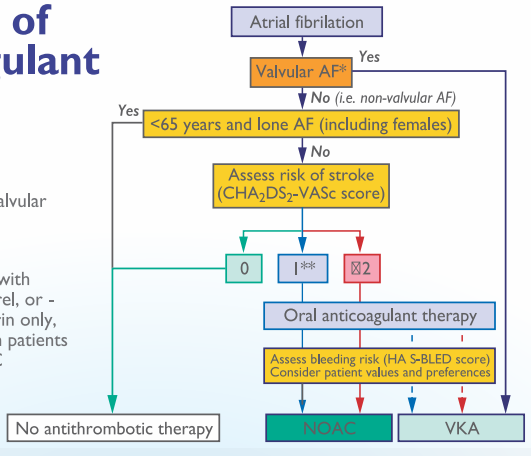

* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or - less effectively - aspirin only, may be considered in patients who refuse any OAC

NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

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The incidence of N1 and N2 metastases in relation to the presence/absence of the peritumoral lymphovascular invasion

Učestalost N1 i N2 metastaza u odnosu na prisustvo/odsustvo limfovaskularne peritumoralne invazije

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ABSTRACT

Introduction: the incidence of N1 and N2 metastases in relation to the presence of peritumoral lymphovascular infiltration and tumor grade in bronchial carcinoma still remains insufficiently researched area that could provide valuable guidance. Several studies have shown a statistically significant difference in the occurrence of N1 and N2 metastases in relation to the type and size of the bronchial carcinoma. The relationship between the occurrence of N1 and N2 metastases and the degree of the tumor immaturity in the bronchial carcinoma remains insufficiently documented. The aim of this research was to determine the frequency of N1 and N2 metastases in relation to the presence/absence of peritumoral lymphovascular invasion, as well as to investigate the relative risk of N metastases development in relation to the presence of peritumoral lymphovascular invasion. Materials and methods: this study included 331 patients of all ages, both men and women, diagnosed with bronchial carcinoma using various diagnostic procedures. In these patients, surgical treatment was indicated and the anatomical resection was performed. Results: a total of 331 patients were included in the study and N1 metastases were present in 39.88% of cases, while N2 metastases were present in 4.53% of cases with bronchial carcinoma. Peritumoral lymphovascular invasion was present in 37.55% of cases (86 out of 229 patients) with N0 disease, in 55.89% of cases (128 out of 229 patients) with N1 disease, and in 6.55% of cases (15 out of 229 patients) with confirmed N2 disease. Conclusion: the presence of the peritumoral lymphovascular invasion is more often accompanied by metastases in corresponding regional lymph nodes. By calculating the total relative risk, there is almost a 30-fold higher risk of developing metastases in N1 and N2 lymph nodes in the presence of peritumoral lymphovascular invasion.

Key words: bronchial carcinoma, lymph node metastases, lymphovascular invasion

SAŽETAK

Uvod: učestalost pojave N1 i N2 metastaza u odnosu na prisustvo limfovaskularne peritumoralne infiltracije te gradus tumora kod bronhalnog karcinoma jedan je od nedovoljno istraženih problema koji može pružiti dragocjene smjernice. Brojni radovi su pokazali da statistički postoji značajna razlika u pojavi N1 i N2 metastaza u odnosu na vrstu i veličinu bronhalnog karcinoma. Povezanost pojave N1 i N2 metastaza i stepena nezrelosti tumora kod plućnog karcinoma je još uvijek nedovoljno dokumentovana. Cilj: odrediti učestalost N1 i N2 metastaza u odnosu na prisustvo/odsustvo limfovaskularne peritumoralne invazije i utvrditi relativni rizik od nastanka N metastaza u odnosu na postojanje peritumoralne limfovaskularne infiltracije. Materijali i metode: istraživanjem je obuhvaćen 331 pacijent svih starosnih skupina oba spola kod kojih je različitim dijagnostičkim procedurama utvrđena dijagnoza plućnog carcinoma i na osnovu toga indiciran i izveden hirurški tretman. Operativni hirurški tretman izveden je na nivou neke od anatomskih resekcija. Rezultati istraživanja: istraživanje je obuhvatilo 331 pacijenta i N1 metastaze su bile prisutne kod 39,88%, a N2 metastaze kod 4,53% pacijenata oboljelih od karcinoma bronha. Limfovaskularna peritumoralna invazija je bila prisutna kod 37,55%(86/229) pacijenta sa N0 bolesti te kod 55,89%(128/229) kod N1 i kod 6,55% (15/229) sa N2 bolesti. Zaključak: dobijeni rezultati pokazuju da prisustvo peritumoralne limfovaskularne invazije češće prate metastaze u odgovarajuće regionalne limfne čvorove. Izračunavanjem ukupnog relativnog rizika je ustanovljeno da postoji skoro 30 puta veća šansa za nastanak metastatskih promjena u limfnim čvorovima (N1 i N2) u prisustvu peritumoralne limfovaskularne invazije.

Ključne riječi: bronhalni karcinom, N metastaze, limfovaskularna invazija

INTRODUCTION

The incidence of N1 and N2 metastases in relation to the presence of peritumoral lymphovascular infiltration and tumor grade in bronchial carcinoma still remains insufficiently researched area that can provide valuable guidance on cancer aggressiveness, disease spread, prognosis and treatment.

Given that each lung lobe has its own lymphatic drainage, metastatic spread of lung cancer by lymphatic route depends on its location. Consequently, understanding the metastatic spread of cancer to regional lymph nodes requires good knowledge of the anatomy of the lymphatic system of each lobe (1).

The influence of numerous factors, i.e. the most common types of lung cancer, tumor size as well as the degree of differentiation and stage of the malignant disease on the occurrence of N1 and N2 metastases has been thoroughly investigated. Several studies have shown a statistically significant difference in the occurrence of N1 and N2 metastases in relation to the type and size of the bronchial carcinoma (2). The relationship between the occurrence of N1 and N2 metastases and the degree of immaturity of the tumor in the bronchial carcinoma remains insufficiently documented (3).

A literature review of available medical databases and research articles was conducted over the past 10 years, but the strong association between the presence of N1 and N2 metastases and pathohistological confirmation of peritumoral lymphovascular invasion (a reliable indicator that correlates with the tumor aggressiveness in bronchial carcinoma) was not observed (4).

AIM

The aim of this research is to determine the frequency of N1 and N2 metastases in relation to the presence/absence of peritumoral lymphovascular invasion, as well as to investigate the relative risk of N metastases development in relation to the presence of peritumoral lymphovascular invasion.

MATERIALS AND METHODS

We analyzed data from patients diagnosed with bronchial carcinoma who underwent surgical resection during hospitalization at Clinic of Thoracic Surgery of the Clinical Center University of Sarajevo in the period from 1 January 2013 to 1 January 2018. In total, this study included 331 patients of all ages, both men and women, diagnosed with bronchial carcinoma using various diagnostic procedures. In these patients, surgical treatment was indicated and the anatomical resection was performed.

The inclusion criteria included a definitive histopathological diagnosis, which at least had to contain data regarding the presence/absence of peritumoral lymphovascular invasion and the lymph node status (N0, N1 or N2).

Patients without a definitive histopathological diagnosis of non-small cell lung cancer and inoperable cases were excluded from the study.

RESULTS

A total of 331 patients diagnosed with bronchial carcinoma underwent surgical resection during their hospitalization at the Clinic of Thoracic Surgery in the period from 1 January 2013 to 1 January 2018. The mean age of the patients was 62.69 ± 7.46.

Histopathololgical findings in relation to the type of bronchial carcinoma are shown in Table 1.

Table 1 **Definitive histopathological diagnoses in relation to the type of bronchial carcinoma.**

Squamous cell carcinoma	54.98%	(182/331)
Adenocarcinoma	42.30%	(140/331)
Large cell carcinoma	2.72%	(9/331)
TOTAL:	100.00%	(331/331)

In our study, the squamous cell carcinoma was the most common type of bronchial carcinoma, found in 54.98% of cases (182 out of 331 patients), followed by adenocarcinoma, found in 42.30% of cases (140 out of 331 patients). The least common type of bronchial carcinoma was large cell carcinoma, found in 2.72% of cases (nine out of 331 patents).

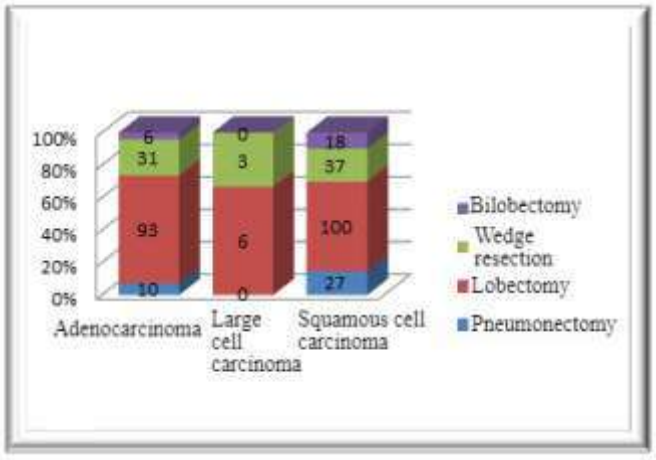

Figure 1 **The relation between the most common histopathological diagnoses and surgical resections.**

Standard lobectomy was the most common surgical resection of both squamous cell carcinoma, i.e. in 54.94% of cases (100 out of 182 patients) and adenocarcinoma, i.e. 66.42% of cases (93 out of 140 patients).

The prevalence of lymph node (N0, N1 and N2) involvement in bronchial carcinoma is shown in Table 2.

Table 2 **The prevalence of lymph node involvement in patients diagnosed with bronchial carcinoma**.

	%	n
N0	55.59%	(184/331)
N1	39.88%	(132/331)
N2	4.53%	(15/331)
TOTAL:	100.00%	(331/331)

The most common were cases without the presence of malignant cells in the lymph nodes (N0), i.e. 55.59% of cases (184 out of 331 patients), N1 metastases were present in 39.88% of cases (132 out of 331 patients), and N2 metastases were observed in 4.53% of cases (15 out of 331 patients).

The relation between N0, N1 and N2 metastases and the most common histopathological diagnoses is shown in Table 3.

Table 3 **The prevalence of N0, N1 and N2 metastases and their relation to the most common histopathological diagnoses**.

	Large cell carcinoma		Squamous cell carcinoma		Adenocarcinoma	
	%	N	%	n	%	n
N0	66.67%	(6/9)	52.75%	(96/182)	58.57%	(82/140)
N1	33.33%	(3/9)	43.96%	(80/182)	35.00%	(49/140)
N2	00.00%	(0/9)	3.30%	(6/182)	6.43%	(9/140)
TOTAL:	100.00%	(9/9)	100.00%	(182/182)	100.00%	(140/140)

More than half of the patients with both squamous cell carcinoma, i.e. 52.75% of cases (96 out of 182 patients) and adenocarcinoma, i.e. 58.57% of cases (82 out of 140 patients) had no lymph node metastases (N0). N1 lymph node involvement (positive ipsilateral hilar lymph nodes) was present in 43.96% of cases with squamous cell carcinoma and in 35.00% of cases with adenocarcinoma. N2 lymph node involvement was present in 3.30% of cases with squamous cell carcinoma and in 6.43% of cases with adenocarcinoma.

The prevalence of the peritumoral lymphovascular invasion and its relation to the lymph node status is shown in Table 4.

Table 4 **The prevalence of the peritumoral lymphovascular invasion and its relation to the lymph node status**.

*PLVI	N0	N1	N2	Total
No	96% (98/102)	3.92% (4/102)	0.98% (1/102)	100% (102/102)
Yes	37.55% (86/229)	55.89% (128/229)	6.55% (15/229)	100% (229/229)
Total	55.58% (184/331)	39.87% (132/331)	4.53%(15/331)	100% (331/331)

*PLVI - peritumoral lymphovascular invasion

Peritumoral lymphovascular invasion was present in 37.55% of cases (86 out of 229 patients) with N0 disease and in 55.89% of cases (128 out of 229 patients) with N1 disease as well as in 6.55% of cases (15 out of 229 patients) with confirmed N2 disease.

Peritumoral lymphovascular invasion was not present in 96% of cases (98 out of 102 patients) with NO disease, 3.92% of cases (4 out of 102 patients) with N1 disease as well as 0.98% of cases (1 out of 102 patients) with confirmed N2 disease.

The frequency of lymph node metastases in relation to the presence of peritumoral lymphovascular invasion is shown in Table 5.

Table 5 **The frequency of lymph node metastases in relation to the presence of peritumoral lymphovascular invasion.**

		Lymph node metastases		
		Yes	No	Total:
Peritumoral lymphovascular invasion	Yes	a=143	b=86	a+b=229
	No	c=4	d=98	c+d=102
Total:		a+c=147	b+d=184	N=331

It is possible to calculate the sensitivity, specificity, positive and negative predictive values of the peritumoral lymphovascular infiltration in relation to the presence of lymph node metastases. Their values were obtained as follows: sensitivity (97.27%), specificity (53.26%), positive predictive value (62.447%) and negative predictive value (96.07%). The overall accuracy was 72.8%.

Data for calculating the relative risk of N1 lymph node metastases in relation to the presence of peritumoral lymphovascular infiltration is shown in Table 6.

Table 6 **The prevalence of N1 lymph node metastases in relation to the presence of peritumoral lymphovascular infiltration.**

		Peritumoral lymphovascular invasion		
		Yes	No	Total
Lymph node involvement	Yes	a=128	b=4	a+b=132
	No	c=86	d=98	c+d=184
Total:		a+c=214	b+d=102	N=316

The risk of lymph node metastases in patients with peritumoral lymphovascular invasion was calculated as follows:
The risk among patients with PLVI = (a/b) = 128/4 = 31.00.
The risk of lymph node metastases in patients without peritumoral lymphovascular invasion was calculated as follows:
The risk among patients without PLVI = (c/d) = 86/98 = 0.87

The study investigated the association between the peritumoral lymphovascular invasion and regional lymph node metastases using Spearman's rank correlation coefficient. There was a statistically significant correlation between the variables, i.e. $\rho = 0.544$, $n = 331$, $p < 0.0001$. The presence of peritumoral lymphovascular invasion was more often accompanied by the presence of metastases in the corresponding regional lymph nodes.

DISCUSSION

The presence of N1 disease significantly affects the five-year survival rate, and it has been observed that the same corresponds to the number of involved N1 lymph nodes (5). The presence of N2 disease is still the subject of much debate, which leads to the fact that most surgeons and oncologists at present opt for a combined approach to N2 NSCLC. It has been shown that patients who have been preoperatively diagnosed with N2 lymphadenopathy do not benefit much from surgical treatment (6). However, patients whose N2 disease is not clearly clinically classified, but diagnosed via surgical treatment or using the histopathological examination, have better postoperative outcomes (7).

Lymph nodes in patients diagnosed with bronchial carcinoma who were treated in this study were not proportionally affected by metastatic spread of the disease as seen from the obtained results. The most common were patients without the presence of malignant cells in the lymph nodes (N0), i.e. 55.59% of cases, N1 metastases were present in 39.88% of cases, and N2 metastases in 4.53% of bronchial carcinoma cases.

Almost similar results have been published in several other literature reports (8). Given the fact that the majority, i.e. 95.47%, of patients who underwent surgical treatment had N0 and N1 lymph node status, it could be assumed and concluded that there was a relatively good diagnostic assessment of patients as well as clinical determination of the disease stage and selection of patients for surgical treatment.

In more than half of the patients, both in the squamous cell population group, i.e. 52.75% of cases (96 out of 182 patients) as well as in the adenocarcinoma population group, i.e. 58.57% of cases (82 out of 140 patients), no lymph node metastases were present.

In relation to the presence or absence of peritumoral lymphovascular invasion in patients diagnosed with bronchial carcinoma, the following results were obtained:

Peritumoral lymphovascular invasion was present in 72.46% of cases (229 out of 316 patients) with the presence of lymph node metastases in 62.44% of cases [N1 metastases in 89.51% of cases (128 out of 143 patients) and N2 in 10.49% of cases (15 out of 143 patients)].

Based on the available data, sensitivity (97.27%), specificity (53.26%), positive predictive value (62.447%) as well as the negative predictive value (96.07%) were calculated. The overall accuracy was 72.8%.

The total relative risk of lymph node metastases in relation to the presence of peritumoral lymphovascular invasion is 35.63, which means that there is a 35.63 times higher chance of developing disease with the lymph node metastasis in the presence of peritumoral lymphovascular invasion compared to when it is not present.

The study unequivocally confirmed that the presence of peritumoral lymphovascular invasion was more often accompanied by the presence of metastases in the corresponding regional lymph nodes. An association between the presence of peritumoral lymphovascular invasion and the frequency of N1 and N2 metastases was observed.

The presence of peritumoral lymphovascular invasion can serve as a good predictor in relation to the assessment of the lymph node status, and indirectly have both prognostic and therapeutic significance for these patients.

However, there are reports in the available literature on other types of malignancies, primarily breast cancer and cervical cancer, in which similar studies (the presence of peritumoral lymphovascular invasion and the lymph node status) have been conducted and shown an association between the peritumoral lymphovascular invasion and more frequent occurrence of lymph node metastases (9,10).

CONCLUSION

Peritumoral lymphovascular invasion was present in 70.52% of cases diagnosed with bronchial carcinoma. Lymph nodes were involved in 70.52% of cases with present lymphovascular invasion and in only 3.30% of cases in which the lymphovascular invasion was not present. Peritumoral lymphovascular invasion was present in 53.26% of cases (143 out of 244 patients) with confirmed N1 disease and in 100% of cases with confirmed N2 disease. By calculating the total relative risk, there is almost a 30-fold higher risk of developing metastases in N1 and N2 lymph nodes in the presence of the peritumoral lymphovascular invasion. The presence or absence of the peritumoral lymphovascular invasion can be used both in predicting and excluding the presence or absence of the lymph node involvement.

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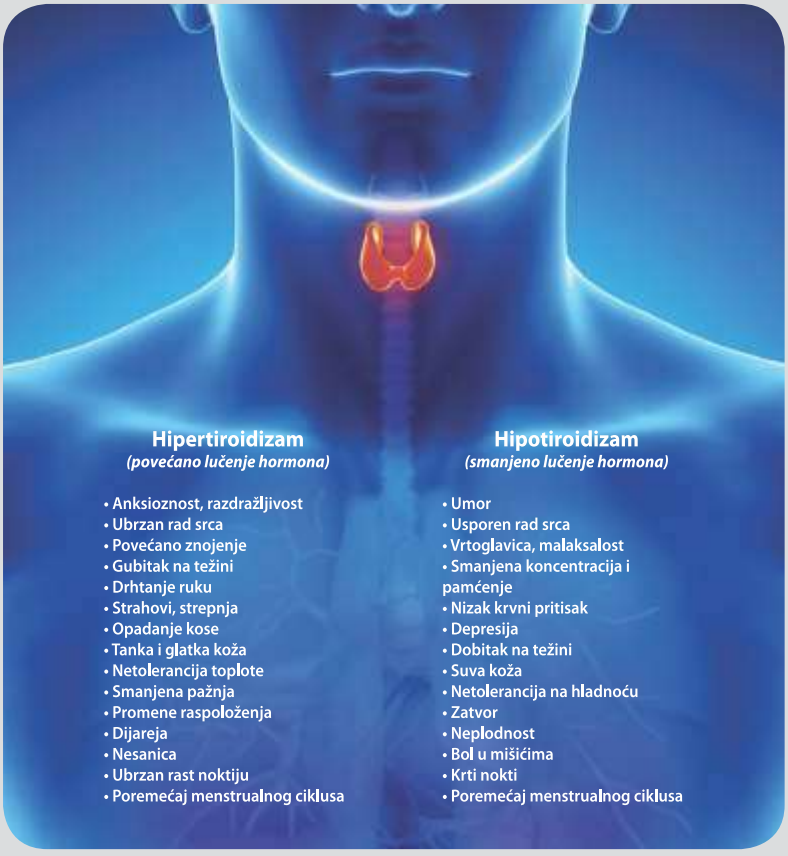

Characteristics of intracranial aneurysms of patients treated at Clinic of Neurosurgery of the Clinical Center University of Sarajevo in a five-year period: morbidity, treatment and outcomes

Karakteristike intrakranijalnih aneurizmi kod pacijenata tretiranih na Klinici za neurohirurgiju Kliničkog centra Univerziteta u Sarajevu u petogodišnjem peridu: morbiditet, tretman i ishodi

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ABSTRACT

Introduction: an intracranial cerebral aneurysm is a focal enlargement of the cerebral blood vessel wall caused by a locally morphologically alteration. According to globally available epidemiological data, cerebral circulation aneurysms are relatively common, with a prevalence ranging from 0.4% to 3.6%. Most studies indicate a significantly higher incidence in women. They most often occur between the ages of 40 and 60. Aim: evaluation of basic epidemiological characteristics of intracranial aneurysms in the population of patients treated at Clinic of Neurosurgery of the Clinical Center University of Sarajevo (CCUS) in a five-year period. Materials and methods: the research was conducted retrospectively for a five-year period from the beginning of 2014 to the end of 2018. The study included 415 patients. The obtained data were processed by methods of descriptive statistical analysis, and the frequency of intracranial aneurysms, sex and age distribution of patients, frequency of aneurysms according to localization and methods and the treatment's final outcomes were analysed. Results: in the mentioned five-year period, 415 patients with intracranial aneurysms were admitted to the Clinic for Neurosurgery. According to gender structure, women made 68,7 % (285) and men 31,3 % (130) with a ratio of 2.2:1 in favour of women. According to the localization, the middle cerebral artery - MCA was present in 105 (25.3%) patients. Anterior communicating artery aneurysms - ACoA were verified in 96 (23.1%) while internal carotid artery aneurysms - ICA were found in 83 (20.0 %) patients. There were 48 (11.6 %) patients with multiple intracranial aneurysms. Regarding the modified Rankin score as a unit of outcome, we had an excellent outcome in 185 (44.6%) patients, while a good outcome was recorded in 76 (18.3%) patients. A poor outcome was recorded in 22 (5.3%) with a total lethal outcome in 132 (31.8 %) patients, predominantly of Hunt Hess scores of IV and V. Conclusion: the female sex is a predisposing factor for the development of intracranial aneurysms, and aneurysms are most often detected between the ages of 50 and 70 in a ruptured form. Contrary to global literature, the most common localization of intracranial aneurysms in the population of our patients is the middle cerebral artery (MCA) followed by aneurysms of the anterior communicating artery (ACoA) and then aneurysms of the internal carotid artery (ICA).

Key words: intracranial aneurysms, localization, treatment, outcomes

SAŽETAK

Uvod: intrakranijalna aneurizma pretstavlja lokalno proširenje zida krvnog suda uzrokovano lokalnom morfološkom alteracijom. Prema svjetski dostupnim epidemiološkim podacima, cerebralne aneurizme su relativno česte sa prevalencom između 0,4 do 3,6%. Većina studija pokazuje povišenu incidencu aneurizmi kod žena koje se obično javljaju u dobi od 40 do 60 godina. Cilj istraživanja: evaluacija bazičnih epidemioloških karakteristika intrakranijalnih aneurizmi u populaciji pacijenata liječenih na Klinici za neurohirurgiju Kliničkog centra Univerziteta u Sarajevu u petogodišnjem periodu. Materijali i metode: istraživanje je provedeno retrospektivno za petogodišnji period od početka 2014. do kraja 2018. godine. U našu studiju je uključeno 376 pacijenata sa verificiranom intrakranijalnom aneurizmom. Dobiveni podaci su obrađeni metodama deskriptivne statističke analize, a analizirala se učestalost intrakranijalnih aneurizmi, spolna i starosna distribucija pacijenata, učestalost aneurizmi prema lokalizaciji, načini kao i krajniji ishodi tretmana. Rezultati: u navedenom petogodišnjem

periodu na Klinici za neurohirurgiju je primljeno 415 pacijenata sa intrakranijalnom aneurizmom. Prema spolnoj strukturi, žena je bilo 68,7% (285), a muškaraca 31,3% (130) sa odnosom 2,2:1 u korist žena. Prema lokalizaciji srednja cerebralna arterija – MCA je bila najzastupljenija i to kod 105 (25,3%) pacijenata. Aneurizme prednje komunikantne arterije – ACoA su verificirane kod 96 (23,1%) dok su aneurizme unutrašnje karotidne arterije – ICA nađene kod 83 (20,0 %) pacijenata. Pacijenata sa multiplim intrakranijalnim aneurizmama je bilo 48 (11,6%). U pogledu modificiranog Rankin score-a kao jedinice ishoda, odličan ishod smo imali kod 185 (44.6 %) pacijenata, dok je dobar ishod zabilježen kod 76 (18.3%) pacijenata. Loš ishod je evidentiran kod 22 (5.3%) pacijenta sa ukupnim letalnim ishodom kod 132 (31.8%) pacijenata, dominatno Hunt Hess skora IV i V. Zaključak: ženski spol je predisponirajući faktor za nastanak intrakranijalnih aneurizmi te se aneurizme najčešće otkrivaju između 50. i 70. godine života u rupturiranoj formi. Oprečno svjestkoj literaturi, najčešća lokalizacija intrakranijalnih aneurizmi u populaciji naših pacijenata je srednja cerebralna arterija iza koje slijede aneurizme prednje komunikantne arterije, a potom aneurizme unutrašnje karotidne srterije.

Ključne riječi: intrakranijalne aneurizme, lokalizacija, tretman, ishodi

INTRODUCTION

An intracranial cerebral aneurysm is a focal enlargement of the cerebral blood vessel wall caused by a locally morphologically alteration mostly in an arterial blood vessel.

Since the 19th century, the treatment of cerebral aneurysms has been one of the greatest challenges in neurosurgery. The first surgery on a ruptured aneurysm (muscle wrapping) was performed by Dott NM in 1933 (1), and the first surgery with the goal of aneurysm occlusion with a clip was performed in 1937 by Dandy WE (2). With the introduction of the intraoperative microscope and the postulates of microneurosurgery in the 1960s, the era of modern treatment of intracranial aneurysms began (3).

According to globally available epidemiological data, cerebral circulation aneurysms are relatively common, with a prevalence ranging from 0.4% to 3.6% in retrospective and prospective autopsy studies, and from 3.7% to 6% in retrospective and prospective angiographic studies. The prevalence obtained from angiographic studies exceeds the true prevalence due to selection bias, while the prevalence of autopsy studies is underestimated due to the impossibility of reviewing the source material. Therefore, it could be said that the prevalence of intracranial aneurysms is about 4% (4,5). Most studies indicate a significantly higher incidence in women (5). They most often occur between the age of 40-60 years (in the first decade of life <1%, in the second decade 2%, in the third 6%, in the fourth 15%, in the fifth 26%, in the sixth 28%, in the seventh 16%, in the eighth 6%) (6).

Classification

According to pathohistological characteristics, aneurysms are divided into sacral (berry, sac), fusiform (longitudinal dilati on of the blood vessel wall), dissecting (stratified blood vessel walls) and Charcot-Bouchard aneurysms (so-called mycotic type). When we talk about cerebral aneurysms, it primarily refers to sacral or berry aneurysms which are the most common (make up 90% of cerebral circulation aneurysms), and localized at the bifurcations of the main cerebral arteries or at the site of separation of their branches, on the ventral side of the brain extracerebral subarachnoid spaces.

According to size, aneurysms can be divided into microaneurysms (largest diameter <3mm), small aneurysms (3-6 mm), medium (7-10 mm), large (11-25 mm) and giant (> 25 mm).

According to localization, cerebral aneurysms are divided into anterior aneurysms and posterior circulation aneurysms. About 85% of aneurysms are located on arteries of the so-called anterior circulations of the Willis circle, while 15-20% of them are located in the vertebrobasilar basin (7). About 15-20% of patients have multiple aneurysms. Aneurysms are most often localized on the anterior communicating artery (AcoA) (35%), on the internal carotid artery (ICA) (30%, including only the internal carotid artery, posterior communicating artery and ophthalmic artery), then on the middle cerebral artery (MCA) (22%), and much less frequently on the posterior circulation arteries (about 15%) where the most common localization is the basilar artery (BA) (the apex of the basilar artery where it branches into the two posterior cerebral arteries (PCA) (7).

Clinical presentation

Most aneurysms are small and asymptomatic, and as such are never detected. Some aneurysms are detected by chance by radiological evaluation of other conditions (e.g. mild trauma, neurological symptoms without correlation with the aneurysm, etc.), and some cause focal neurological symptoms by compression of the cranial nerves or brain tissue (usually larger than 20 mm). However, most aneurysms are detected after their rupture. Each year, about 30,000 people in the United States experience aneurysm rupture, most commonly in the sixth decade of life (8).

The most common clinical manifestation of intracranial aneurysm rupture is subarachnoid hemorrhage (SAH) with its typical presentation: severe headaches ("the strongest headache in life"), nausea, vomiting, neck stiffness, disturbance of consciousness and seizures (7,8). Aneurysm rupture can also be manifested by the formation of an intracranial hematoma, most often associated with SAH. This type of bleeding accounts for about 1/3 of spontaneous intracranial bleedings. The incidence of SAH is 9-11 / 1,000.000 inhabitants. The main risk factors are: hypertension, predisposition and smoking (7). Bleeding from cerebral aneurysms is the cause of subarachnoid hemorrhage in about 80% of cases, while arteriovenous malformations are the cause of 5% of cases of SAH. If the high incidence of intracranial aneurysms in the general population is compared with the relatively low incidence of SAH, it is clear that only a small fraction of intracranial aneurysms rupture. SAH is usually a devastating event, accompanied by varying degrees of vasospasms, with significant morbidity and mortality (25% to 50%). About 50% of survivors have a permanent disability, and one-third of patients have a positive outcome (7,8).

Diagnostics

A head computed tomography (CT) is the diagnostic of choice when intracranial hemorrhage is suspected. In SAH, CTs are positive

in 95% of cases in terms of visualization of SAH, and the distribution of the bleeding itself may indicate the most likely localization of the aneurysm (8). Further diagnostic protocol involves CTA or MRA of blood vessels of the brain which can clearly visualize the aneurysm, with CTA being a superior and more readily available method. The gold standard in diagnostics is still DSA - digital subtraction angiography which provides the most data: presence or absence of aneurysms, existence of multiple aneurysms, clear presentation of the aneurysm's anatomy (neck, domus, place of rupture), relation to the main blood vessel, the presence of perforators, development of the collateral and the presence and degree of vasospasms (9).

AIM

To present experience of the Neurosurgical Department in the treatment of intracranial aneurysms over a period of five years.

MATERIALS AND METHODS

A retrospective, clinically applied, descriptive study was conducted at Clinic of Neurosurgery of the CCUS in the period from January 2014 to late December 2018. The data source are medical histories of patients with radiologically verified intracranial aneurysms (CT, CTA and in some cases DSA of blood vessels of the brain). The data were analysed using descriptive statistical methodology and presented through diagrams, as well as compared with data from contemporary international studies. We analysed the frequency of intracranial aneurysms in the total population of neurosurgical patients, the sex and age distribution of patients, the frequency of aneurysms according to localization, and treatment modalities as well as the outcomes of the treatment of patients. Each patient was treated with one or a combination of different treatment modalities: microsurgical occlusion, endovascular occlusion, external ventricular drainage, or conservative treatment. Small unruptured aneurysms can be observed, but most aneurysms require some form of active treatment. Today, there are two ways to actively treat intracranial aneurysms: microsurgical and endovascular. The outcome of treatment of patients is assessed on the basis of a modified Rankin score (mRs) according to which patients are classified into one of 4 categories: values 0-1 correspond to an excellent outcome, 2-3 is a good outcome, 4-5 is bad, while 6 represents a fatal outcome.

RESULTS

During the five-year period of the study (from January 2014 to the end of December 2018), a total of 5,615 (σ = 113.48) patients were admitted to Clinic of Neurosurgery of the CCUS (2014: 1059, 2015: 938, 2016:1146, 2017: 1238, 2018:1234 patients), of which 415 were patients with verified cerebral blood vessel aneurysm. Those patients represent 7.4 % of general neurosurgical patients. The average number of admitted patients with intracranial aneurysm is 75.2 (± 8), which classifies the Clinic of Neurosurgery in the so-called high-volume cerebrovascular center. Twelve patients were not treated at all. They either refused treatment or decided to be treated in another institution, and thus were not included in our study.

Out of the total number of patients with intracranial aneurysms included in the study, 285 patients were female (68.7%) and 130 male patients (31.3%). The female/male ratio was 2.2. Statistical analysis using Student t test indicate statistically significant deviation from the expected distribution of gender in the sample (t=7-892; p=0.0001; p<0.01).

It is observed that the female sex is represented in cca. ¾ of cases. Given that these are predominantly ruptured aneurysms, the female sex is a risk factor for the occurrence as well as for the rupt ure of an intracranial aneurysm.

Patients were stratified into four age groups: Group I; 30 years and younger, Group II; from 31 to 50 years, Group III from 51 to 70 years and Group IV; 70 years and older. A total of 10 patients (2.4% of the total number of patients) were aged 30 and below, of which 1 were men (0.8% of the total number of men) and 9 were women (3.2% of the total number of women), of which the male / female ratio in this age group was 1:9. There were a total of 128 patients (30.8% of the total number of patients) aged 31 to 50, of which 40 were men (30.8% of the total number of men) and 88 were women (30.9% of the total number of women). In age group III we have found a total of 229 (55.2%) patients, of which 71 were men (54.6% of the total number of men) and 158 women (55.4% of the total number of women), male/female ratio 1:2.2. There were 48 (11.6%) patients aged 70 and above, 18 men (13.8% of the total number of men) and 30 women (10.5% of the total number of women), male/female ratio 1:2.

Regarding the localization of aneurysms in our patients, a total of 393 (94,99 %) aneurysms in anterior and 22 (5,30 %) in posterior circulation were verified, while there were 48 cases of multiple aneurysms as a separate group (11,56 %). 105 aneurysms (25.3 %) were located on MCA, 96 (23,1 %) on AcoA, 83 (20,0 %) aneurysms were localized on ICA, 18 in BA (43 %), 17 (4,1 %) on PCoA (posterior communicating artery), 11 (2.7%), on PICA (posterior inferior cerebellar artery), 1 (0,2 %) on PCA (posterior cerebral artery) and 5 (1.2 %) in ACA (anterior cerebral artery). Contrary to global literature, MCA aneurysms are dominant in Bosnian population treated at Clinic of Neurosurgery of the CCUS, followed immediately by ACoA aneurysms. In third place are ICA aneurysms with the sub classification at the origin. The data are presented in Figure 1 and Table 1.

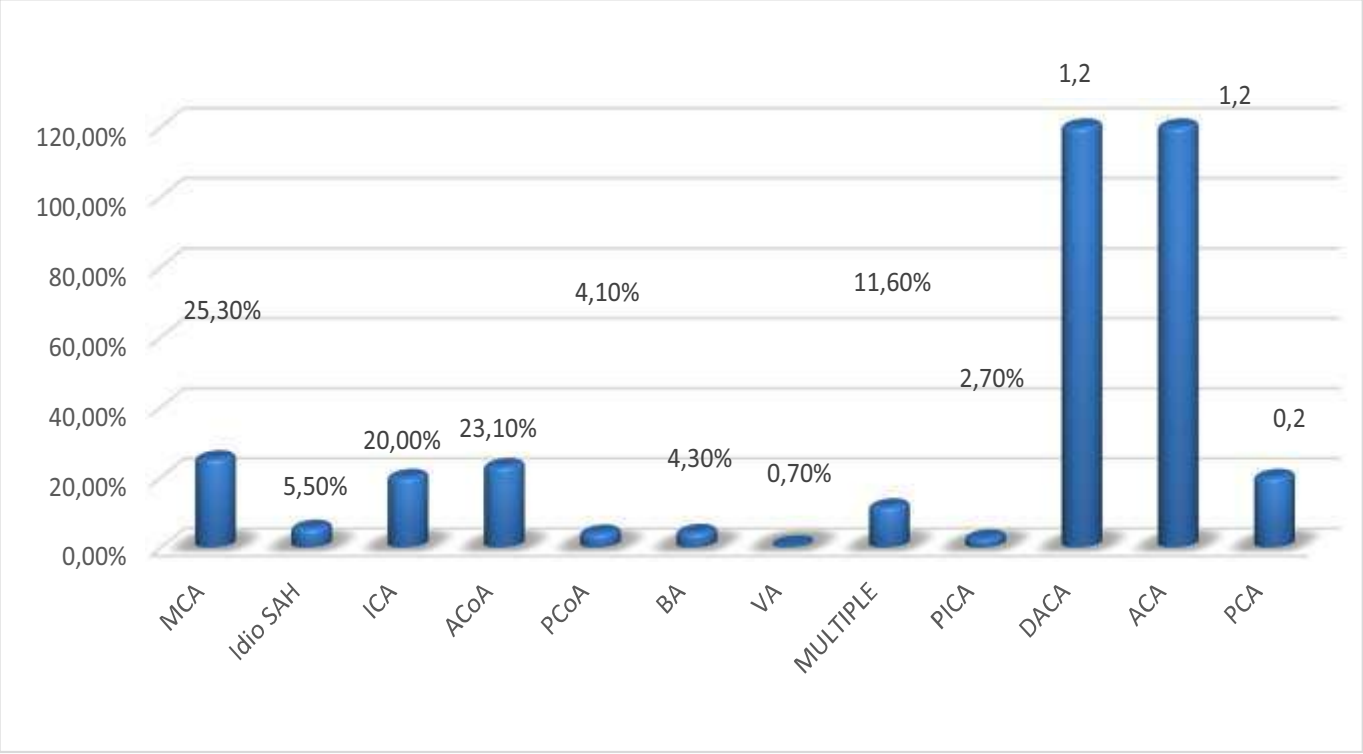

Figure 1 **Frequency of individual localisations of intracranial aneurysms.**

MCA – middle cerebral artery, Idio SAH – idiopathic subarachnoid hemorrhage; ICA – Internal carotid artery; ACoA – anterior communicating artery; PCoA – posterior communicating artery; BA – basilar artery; VA – vertebral artery; MULTIPLE – multiple aneurysms; PICA – posterior inferior cerebellar artery; DACA – distal anterior cerebral artery; ACA – anterior cerebral artery; PCA – posterior cerebral artery

Table 1 **Total number of aneurysms verified in the study**.

		Frequency	Percent
Valid	MCA – medial cerebral artery	105	25.3
	Idio SAH – idiopathic bleeding	23	5.5
	ICA – internal carotid artery	83	20.0
	ACoA – anterior cerebral artery	96	23.1
	ACoP – posterior communicating artery	17	4.1
	BA – basilar artery	18	4,3
	VA – vertebral artery	3	.7
	MULTIPLE - multiple aneurisms	48	11.6
	PICA – posterior inferior cerebellar artery	11	2.7
	DACA – A2 A5 segment of the ACA	5	1.2
	ACA – anterior cerebral artery	5	1.2
	PCA – posterior cerebral artery	1	.2
	Total	415	100.0

Noticeable is the MCA dominance in Bosnian population treated in our department, possibly a unique worldly case. Additional exceptions are ICA aneurysms, which are in our study at third instead of second place by current literature. Patients with diagnosed aneurysms may undergo a variety of treatment modalities, which includes surgical occlusion, endovascular coiling, external ventricular drainage (EVD), and conservative medical treatment. Patients can be treated by a single standalone modality or with a combination of treatment modalities.

The clinical outcome was assessed according to the modified Rankin scale (mRS). For the sake of easier interpretation, mRS is ranked into four categories: values 0-1 correspond to an excellent outcome, 2-3 is a good outcome, 4-5 is a bad outcome, while 6 represent a fatal outcome. According to mRS, 185 (44.6%) patients had an excellent outcome in general, a good outcome was recorded in 76 (18.3%) patients, a poor outcome in 22 (5.3%) cases, with a total lethal outcome in 132 (31.8%) of cases predominantly in groups Hunt Hess IV and V. Clarification of each outcome according to clinical results was the subject of another study by our Clinic and was not specifically analysed in this study.

Most patients have an excellent outcome according to the modified Rankin score. Still 1/3 of patients end up with lethal outcomes in cases of aneurysm rupture especially in cases of Hunt Hess score IV and V.

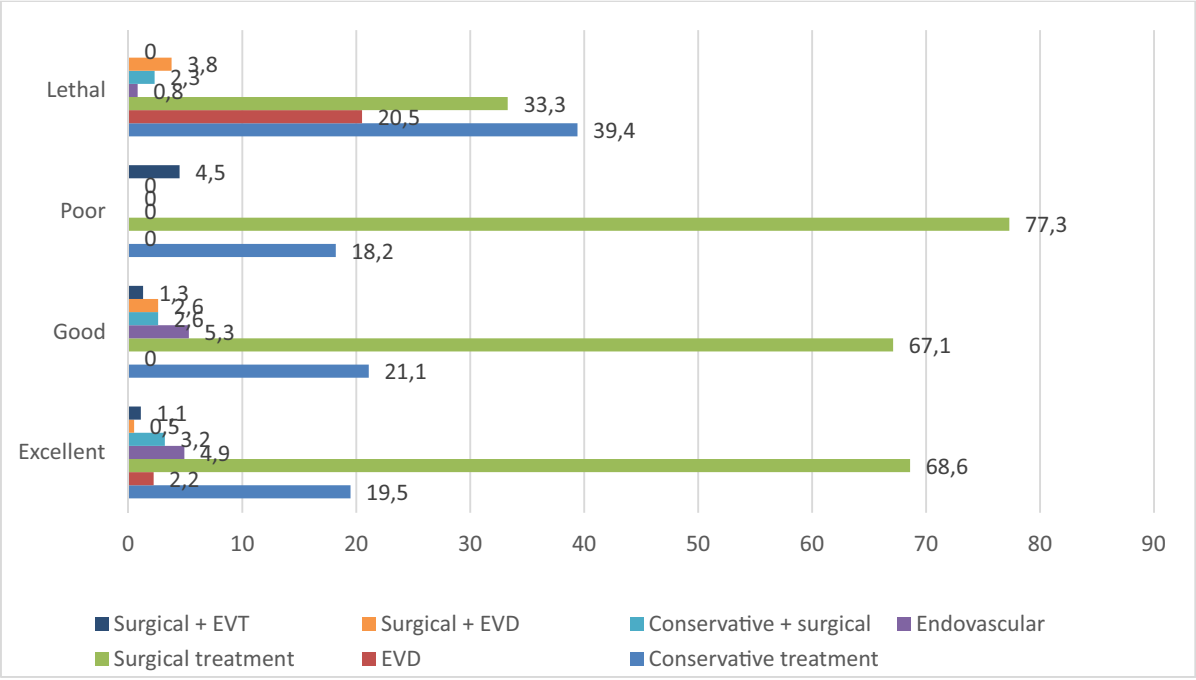

Figure 2 **Different treatment modalities outcome presented in percentage**.

Majority of the patients with lethal and poor outcome were from the Hunt Hess IV and V groups and high Fisher grades.

Among the total number of patients with excellent outcome (n=185) the majority 127 or 68.6% had a surgical treatment. Out of the total of patients with good outcome (n=76) also prevail the patients who were treated with surgical treatment 51 or 67.1%, but also among the patients with poor outcome (n=22) 17 or 77.3% were treated surgically.

Lethal outcome had a total of 132 patients among which the majority were treated by conservative methods due to deep comatose state (n=52 39.4 %). Most of the patients with lethal outcome are found in Hunt Hess groups IV and V which is the topic of our other study.

Statistical analysis using chi squared test indicate that there is a significant difference in the treatment outcome in relation to the type of treatment ($p<0.01$).

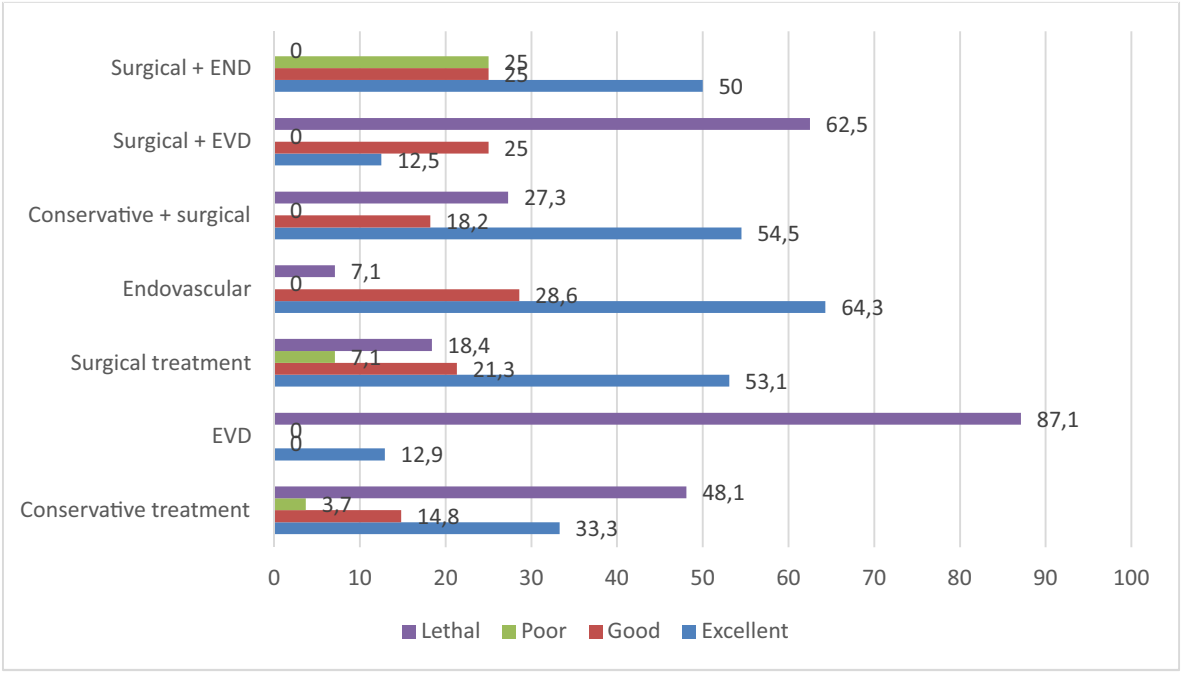

Figure 3 **Percentage of outcome for different aneurysm treatment modalities**.

The highest number of excellent results was recorded in the group treated with endovascular treatment 64.3% followed by a combination of conservative and surgical 54.5 or surgical alone in 53.1%. Endovascular treatment in full form was started in 2020 in our center and these results are not representative. This kind of treatment is done sporadically in strongly selected and mainly nonruptured cases. Further studies should investigate influence and outcome of endovascular results compared to other treatment modalities. The highest proportion of deaths (87.1%) was in the group treated only with EVD followed by a combination of EVD and surgery in 62.5% and conservative treatment in 48.1%.

			C	EVD	S	END	C + S	EVD + S	S + END	Total
Outcome	E	C	36	4	127	9	6	1	2	185
		%	33.3	12.9	53.1	64.3	54.5	12.5	50.0	44.6
	G	C	16	0	51	4	2	2	1	76
		%	14.8	0.0	21.3	28.6	18.2	25.0	25.0	18.3
	B	C	4	0	17	0	0	0	1	22
		%	3.7	0.0	7.1	0.0	0.0	0.0	25.0	5.3
	L	C	52	27	44	1	3	5	0	132
		%	48.1	87.1	18.4	7.1	27.3	62.5	0.0	31.8
Total		C	108	31	239	14	11	8	4	415
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Figure 4 **Correlations: outcome in the treatment modality**.

Legend: E – excellent outcome; G – good outcome; B – bad outcome; L – lethal outcome; C – conservative treatment; EVD – ventriculostomy; S – surgery; END – endovascular treatment; C + S – conservative treatment followed by surgery; EVD + S – ventriculostomy followed by surgery; S + END – surgery and endovascular treatment combined.

If we group the surgical treatment alone or combined with other types of treatment on the one side and non-surgical treatment on the other side we can see that there was 262 or 63.1% surgically treated patients and 153 or 36.9% of non-surgically treated patients.

Excellent outcomes were recorded in 136 or 73.5% of surgically compared to 49 or 26.5% of non-surgically treated patients. Good outcome was recorded in 56 or 73.7% of surgically and 20 or 26.3% of non-surgically treated patients. Poor outcome was also more often recorded in surgically treated patients in 18 or 81.8% compared to 4 or 18.2% of non-surgically treated patients. Lethal outcome however was more common among non-surgically treated patients in 80 or 60.6% compared to 52 or 39.4% surgically treated patients. Statistical analysis using chi squared test indicates that there is a significant difference in treatment outcome in relation to the type of treatment ($p<0.01$)

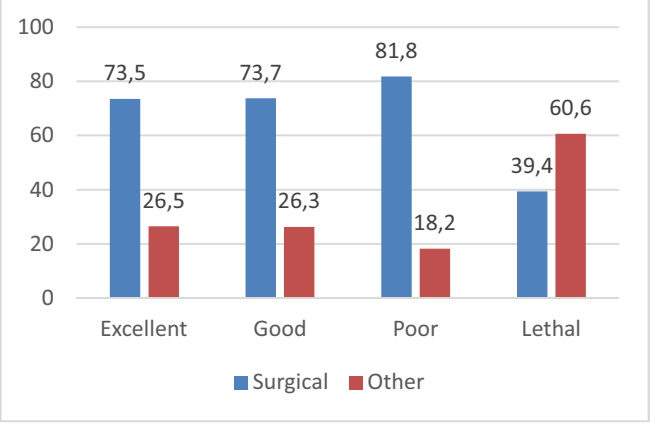

Figure 5 **Graphic comparisons between treatment modalities. Blue columns represent surgical treatment while red columns represent other types of treatment**.

Crosstab

			Surgical	Other	Total
Outcome	E	Count	136	49	185
		% within Surgical treatment	73.5	26.5	44.6
	G	Count	56	20	76
		% within Surgical treatment	73.7	26.3	18,3
	B	Count	18	4	22
		% within Surgical treatment	81.8	18.2	5.3
	L	Count	52	80	132
		% within Surgical treatment	39.4	60.6	31.8
Total		Count	262	153	415
		% within Surgical treatment	63.1%	36.9%	100.0%

Correlation analysis using Spearman coefficient of rank correlation of all factors on the outcome indicate that the age is showing negative impact on the treatment outcome (rho=-0.272; p=0.0001), as well as the score on the Hunt Hess (rho=-0.591; p=0.0001) and the Fisher scale (rho=-0.492; p=0.0001). Location did not show any influence on the treatment outcome (rho=0.013; p=0.787). The type of treatment is showing strong negative correlation (rho=-0.259; p=0.0001) in terms that the patients treated with conservative methods are more likely to have poor or lethal outcome than the patients treated with the surgical treatment.

Correlations

			Outcome	Age	Hunt Hess	Fisher	Location	Treatment modal.	Surgical treatment
Spearman's rho	Outcome	Correlation Coefficient	1,000	,272**	,591**	,492**	,013	-,259**	,279**
		Sig. (2-tailed)	.	,000	,000	,000	,787	,000	,000
		N	415	415	415	415	415	415	415
	Age	Correlation Coefficient	,272**	1,000	,217**	,187**	,052	-,067	,025
		Sig. (2-tailed)	,000	.	,000	,000	,286	,173	,617
		N	415	415	415	415	415	415	415
	Hunt Hess scale	Correlation Coefficient	,591**	,217**	1,000	,649**	-,003	-,077	,067
		Sig. (2-tailed)	,000	,000	.	,000	,951	,116	,175
		N	415	415	415	415	415	415	415
	Fisher scale	Correlation Coefficient	,492**	,187**	,649**	1,000	,009	,024	-,056
		Sig. (2-tailed)	,000	,000	,000	.	,862	,626	,257
		N	415	415	415	415	415	415	415
	Location	Correlation Coefficient	,013	,052	-,003	,009	1,000	,066	-,028
		Sig. (2-tailed)	,787	,286	,951	,862	.	,179	,575
		N	415	415	415	415	415	415	415
	Treatment modality	Correlation Coefficient	-,259**	-,067	-,077	,024	,066	1,000	-,783**
		Sig. (2-tailed)	,000	,173	,116	,626	,179	.	,000
		N	415	415	415	415	415	415	415
	Surgical treatment	Correlation Coefficient	,279**	,025	,067	-,056	-,028	-,783**	1,000
		Sig. (2-tailed)	,000	,617	,175	,257	,575	,000	.
		N	415	415	415	415	415	415	415

**Correlation is significant at the level of 0.01 (2-tailed).

DISCUSSION

In our study, we conducted an epidemiological analysis of patients admitted to the Neurosurgery Clinic in the five-year period from the beginning of 2014 to the end of 2018. The study included a total of 415 patients who radiologically confirmed the presence of an intracranial aneurysm. This means that the average number of patients treated at our Clinic makes the CCUS a high-volume center for the treatment of cerebrovascular morphological lesions in Bosnia and Herzegovina.

Analysing the sexual distribution of patients, we found that intracranial aneurysms are significantly more common in women by 2.2 times in ratio, which corresponds to the data of most current international studies dealing with this issue. According to the sex predominance, the female sex is one of the predisposing factors for the development and the presence of intracranial aneurysms. Thus, according to larger studies sex predominance varies. In Finland, the percentage of women with intracranial aneurysms is 54% (10), in China 62% (10), in Japan 68% (11), in North America and Europe 72% (12) and in Brazil 77, 6% (13).

The most represented age group was from 51 to 69 years and women are more represented than men in all age groups, which is in accordance with the data of international epidemiological studies (6,7,10). It is noticed, that female/male ratio is higher as the patient is younger. For example, female/male ratio in group I (≤30) was found 9:1 comparing to the 1:2 in age group IV (≥70). Correlation analysis using Spearman coefficient of rank correlation of all factors on the outcome indicate that the age is showing negative impact on the treatment outcome (rho=-0.272; p=0.0001), as well as the score on the Hunt Hess (rho=-0.591; p=0.0001) and the Fisher scale (rho=-0,492; p=0.0001).

In our study, as it correlates with others, anterior circulation aneurysms were significantly more common than posterior circulation aneurysms (92.05 % vs. 7.95 %), while cases of multiple aneurysms are found in 11.6% (7). Gasparotti, et al. published similar data back in 2005. The most common localizations of intracranial aneurysms in our study were MCA (26.10%) and ACoA (25.80%), followed by ICA (19.7%), then followed by other less common localizations. These results show a deviation from larger international studies, according to which ACoA aneurysms are in the first place in terms of frequency, followed by ICA, and MCA aneurysms are in the third place (4,5,7). Explaining why MCA aneurysms are most prevalent in the population of Bosnia and Herzegovina stays mystery and it could be probably unique worldly case. One possible explanation is that most ruptured MCA aneurysms are presented with an intracerebral hematoma, which brings patients to the doctor

at an earlier period and requires urgent surgical treatment. More of epidemiological studies should provide an answer about intracranial aneurysm localisation deviation of our population. In final, location did not show any influence on the later treatment outcome (rho=0.013; p=0.787).

In terms of treatment options, microsurgical occlusion of the ruptured aneurysms is still dominant in our case. This treatment modality was used to treat 63.13% of patients with an excellent or good outcome in most of treated patients (73.5 % of cases). Since present date, surgery still provides best results in our population. The type of treatment in general is showing strong negative correlation (rho=-0.259; p=0.0001) in terms that the patients treated with conservative methods are more likely to have poor or lethal outcome than the patients treated with the surgical treatment.

CONCLUSION

The female sex is a predisposing factor for the development of intracranial aneurysms, and they are mostly detected a decade range later in our population which is between the ages of 50 and 70 in a ruptured form. Contrary to the world literature, the most common localization of intracranial aneurysms is the middle cerebral artery (MCA) which could be possibly a unique worldly case. Treatment outcome of surgically treated patients shows better results in terms of final outcome compared to general results. Considering the number of treated patients as well as the outcomes, Clinic of Neurosurgery of the CCUS is one of the "high-volume" centers in the field of cerebrovascular lesions. The formation of cerebrovascular teams in the existing number of neurosurgeons, with additional technical support, would create ideal conditions for the proclamation of the first referral center in the field of cerebrovascular surgery in the state of Bosnia and Herzegovina.

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Fetal echocardiography as a tool in hands of perinatologist

Fetalna ehokardiografija kao alat u rukama perinatologa

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ABSTRACT

Early fetal echocardiography is a method performed as part of ultrasound screening of the fetus between the 11th and 14th week of gestation, while better visualization of the anatomical structures of the heart is possible between the 18th and 22nd week of gestation. Modern pediatric cardiology today deals mainly with congenital heart defects (CHD). Genetic factors determine the normal development of the heart, while embryogenesis takes place between the 18th and 38th day of intrauterine life. Proper performance of fetal echocardiography is an imperative, and it is recommended that it has to be established as a highly important part of the pregnant women examination. It is also important for the preparation of the fetus for possible correction of the CHD and planning of the therapeutic modality by a pediatric cardiologist. The aim of this paper is to present the importance of the use of fetal echocardiography in everyday clinical work.

Key words: congenital heart defects, echocardiography, screening

SAŽETAK

Rana fetalna ehokardiografija je metoda koja se radi u sklopu ultrazvučnog screeninga fetusa između 11. i 14. nedjelje gestacije, a bolja vizuelizacija anatomskih struktura srca je moguća u periodu između 18. i 22. nedjelje gestacije. Moderna pedijatrijska kardiologija se danas bavi uglavnom urođenim anomalijama srca. Genetski faktori određuju normalan razvoj srca, a sama embriogeneza se odvija izmedju 18.-38. dana intrauterinog života. Pravilno izvođenje fetalne ehokardiografije je imperativno, te se preporučuje da se etablira kao još jedna dijagnostička metoda u obradi trudnice. Važna je i za pripremu ploda za eventualnu korekciju urođene anomalije srca, te je i od esencijalnog značaja za planiranje terapeutskog modaliteta od strane pedijatrijskog kardiologa. Cilj rada je prikazati značaja upotrebe fetalne ehokardiografije u svakodnevnom kliničkom radu.

Ključne riječi: urođene anomalije srca, ehokardiografija, probir

INTRODUCTION

Modern pediatric cardiology today deals mainly with congenital heart defects (CHD) of which incidence is from 0.8% to 1% (1). Genetic factors determine the normal development of the heart, while embryogenesis of the heart takes place between the 18th and 38th day of intrauterine life (2,3). The aim of this paper is to present the importance of the use of fetal echocardiography in everyday clinical work.

Anamnesis in mother and congenital heart defects

The most common congenital anomalies are CHDs (30%) (1,2). Often the simplest CHDs have associated anomalies of other organ systems or occur as part of a genetic syndrome (one third of children with CHDs) (4,5,6). As mentioned, the incidence is 0.8-1%, in stillborn children 2%, and in spontaneously terminated pregnancies 10-25% (1,2). Every year, 1.35 million newborns with CHDs are born in the world (7).

Inheritance of cardiac anomalies is a significant problem due to the relatively high frequency compared to other congenital anomalies, but also due to the high frequency of extracardiac malformations in children with CHDs (5). CHDs are anomalies caused by external and/or internal (genetic) factors. Today, almost one-half of all associated noncardiac abnormalities are thought to be chromosomal abnormalities, either autosomal or sex chromosome

aneuploidies, while the others are hereditary and non-hereditary syndromes. The probability of accidental defects is very small (8). This shows the importance of well-taken and documented anamnesis.

Teratogenic factors in pregnancy that can lead to CHDs are: infections (Rubella, Cytomegalovirus), drugs (lithium, thalidomide, trimethadione, anticonvulsants, retinoic acid, amphetamines, progesterone, steroids), disease of mother (diabetes mellitus, phenylketonuria, systemic lupus erythematous) and exposure to X-rays (8). Habits of mother have a significant impact on pregnancy outcome (alcoholism, drug addiction, nicotinism) (8). For example, increased alcohol intake during pregnancy can cause fetal alcohol syndrome, in which patent ductus arteriosus, ventricular septal defect and Tetralogy of Fallot are very common. Comorbidities such as diabetes mellitus are associated with higher risk of CHD, such as transposition of the great arteries, patent ductus arteriosus, ventricular septal defect and cardiomyopathies.

Medical doctors should ask about medications taken during pregnancy, as well as information about the mother's comorbidities. Careful family history should be focused on diseases that are in relation with atherosclerosis and cerebrovascular incidents (hypercholesterolemia and thrombophilia) or muscle diseases (muscular dystrophy, dermatomyositis, familial metabolic cardiomyopathies).

Prenatal (preventive) cardiology is very important and consists of fetal echocardiography and fetal interventional cardiology. The basic need for fetal echocardiography is determined by factors that increase the risk of prenatal heart disease development, and they are actually indications for fetal echocardiography. They are most often divided into two groups: the group of inherited risk factors (family-related) where previous CHD in the family and diseases of the pregnant woman are included, and the group of pathological findings in pregnancies, referred to as fetal factors. Family-related factors are CHDs in a parent, previous child, or fetus with CHD, chromosomal abnormalities, genetic disorders, or syndromes with CHD or cardiomyopathy (9,10). Fetal-related factors include suspicion of CHD or disease during gynecological examination, fetal hydrops, hydrothorax, extracardiac malformation (omphalocela, diaphragmatic hernia, duodenal arthrosis, tracheo-esophageal fistula, cystic hygroma), chromosomopathies and thickening of the archaeal region, which is known to cause heart failure (well vascularized tumors, arteriovenous fistulas, venous insufficiency, feto - fetal transfusion, anemia) (4,5,10,11,12).

Fetal echocardiography

Given the data on the presence of CHD in the general population, the fact that prenatal detection of CHD is of great importance should be emphasized. It is estimated that 25% of neonatal deaths in the first week of life are due to undiagnosed CHD (4). In case of suspicion of certain CHD, it is necessary to conduct an extensive analysis using the fetal echocardiography.

Early fetal heart examination is a method performed as part of an ultrasound screening of the fetus between the 11th and 14th weeks of gestation. Better visualization of the anatomical structures of the heart is between the 18th and 22nd weeks of gestation, and its proper performance is crucial, so many guidelines recommend this period for its performance (4). Fetal echocardiography is indicated in high-risk pregnancies where the chances of fetus having a CHD are likely to be high (Table 1) (12,13,14).

Table 1 **Risk of CHDs (15,16,17).**

Congenital heart defect	Incidence (per 1.000 live birth) (%)	Recurrence risk one sibling affected (%)	Two siblings or mother affected (%)	Father affected (%)
AVSD	0.35	3-4	10-14	1
VSD	1.1-3.57	3	6-10	2-3
HLHS	0.14-0.27	2-3	6-10	-
TA	0.03-0.08	1	3	-
TAPVC	0.06-0.09	0	-	-
Ebstein anomaly	0.06-0.11	1	3-6	
DOLV	-	0	-	-
ToF	0.42	2.5	8	1-2
TA	0.05-0.11	1	3	-
DORV	0.16	2.5	8	-
PS or PA	0.16-0.26	1-2	3-6	-
TGA	0.24-0.32	1.5	5	-
CoA	0.14-0.41	2	4-6	2-3

AVSD- atrioventricular septal defect, VSD- ventricular septal defect, HLHS- hypoplastic left heart syndrome, TA- tricuspid atresia, TAPVC - total anomalous pulmonary venous connection, DOLV- double-inlet left ventricle, ToF- Tetralogy of Fallot, TA - truncus arteriosus, DORV - double-outlet right ventricle, PS or PA - pulmonary stenosis or artresia, TGA- transposition of great arteries, CoA - coarctation of Aorta.

The basic examination in the analysis of the cardiac anatomical structure is the examination of the four-chamber view (Figure 1). This view of the heart gives an overview of the heart cavities; however, it is insufficient for the detection of all forms of CHD, such as transposition of great arteries, Tetralogy of Fallot, double-outlet right ventricle, or truncus arteriosus. By showing the origin of large blood vessels (three vessel view) (Figure 2), the analysis of the complete cardiac anatomy is achieved, as well as the detection of cardiac anomalies with 85% success rate obtained (15,16,17,18).

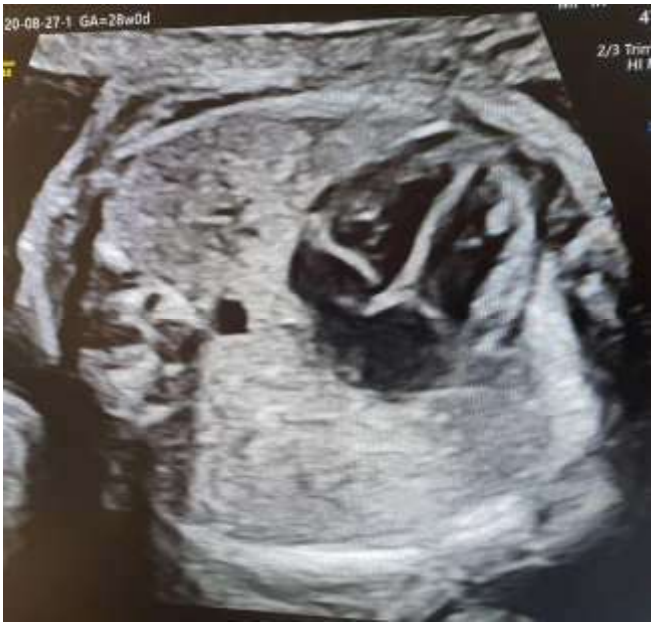

Figure 1 **Four-chamber view.**

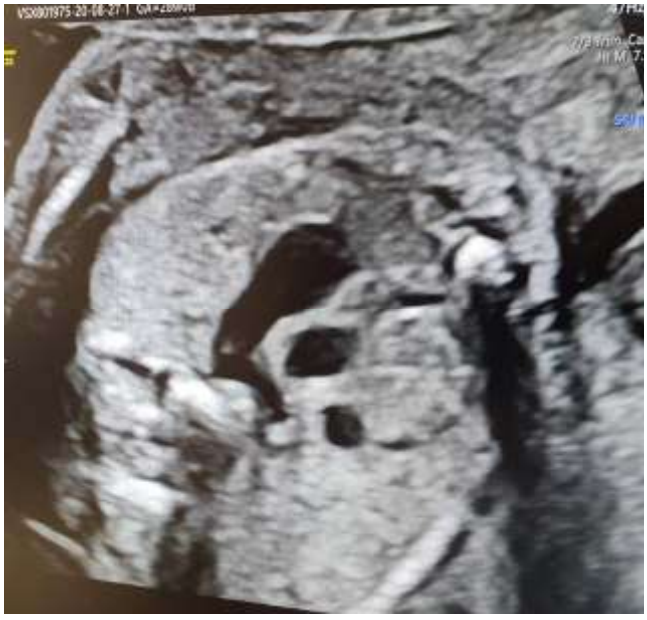

Figure 2 **Three-vessel view.**

Early detection of CHD helps to make very important decisions, such as the decision to terminate pregnancy, planning the time of delivery, choosing a tertiary level institution as the place of birth and treatment of neonatus, introducing parents to the condition of the fetus before birth, and implementing certain therapeutic procedures in utero (19). The aim of fetal echocardiography is to answer the question as to the existence or non-existence of a fetal heart defect.

Peculiarities of examination as part of fetal heart analysis

Fetal echocardiopgraphy requires a well-trained sonographer as well as the use of ultrasound devices that can perform the techniques of Color Doppler (Figure 3, Figure 4), M-mode echocardiography, 3D and 4D ultrasonography. Every obstetrician should have the ability of basic fetal heart analysis, but fetal echocardiography requires special education in this area as well as the training of sonographers (15).

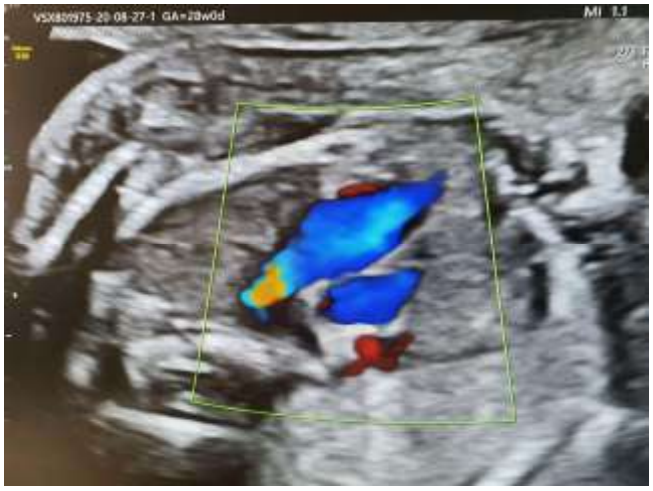

Figure 3 **Three-vessel view - Color Doppler.**

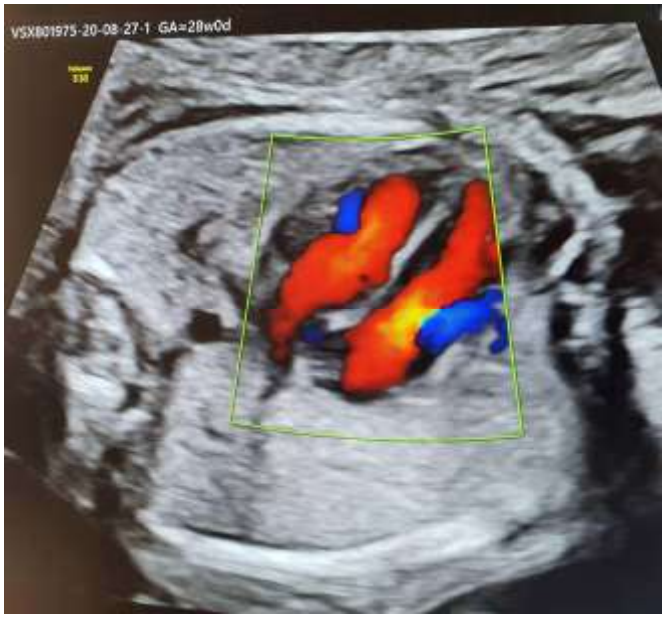

Figure 4 **Color Doppler as a method during examination.**

The basic cardiac structures to be evaluated by fetal echocardiography are:

1. four chamber view (evaluation of heart cavities);
2. evaluation of atrial and ventricular septum by Color Doppler;
3. evaluation of left ventricular outflow tract;
4. evaluation of right ventricular outflow tract;
5. three-vessel view (pulmonary trunk (oblique axis) anterior and leftward, aorta (short axis) and pulmonary artery (short axis);
6. evaluation of short axis view (ventricles, aorta and pulmonary artery) (Figure 5);
7. evaluation of aortic arch (Figure 6, Figure 7);
8. evaluation of ductal arch;
9. evaluation of superior and inferior vena cava.

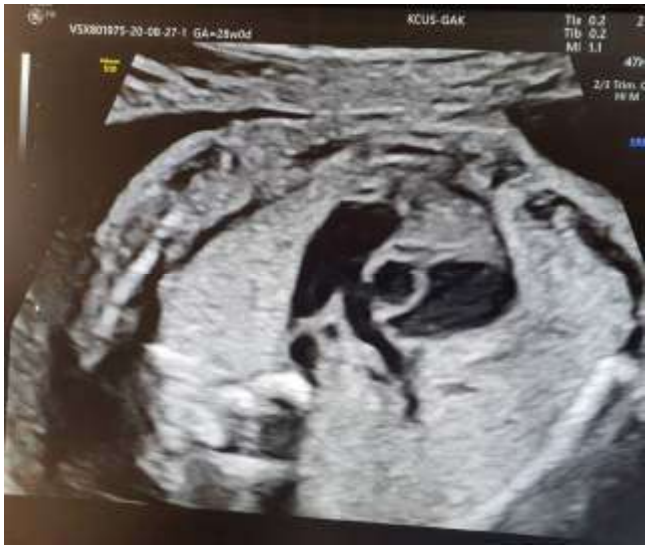

Figure 5 **Pulmonary artery with branches.**

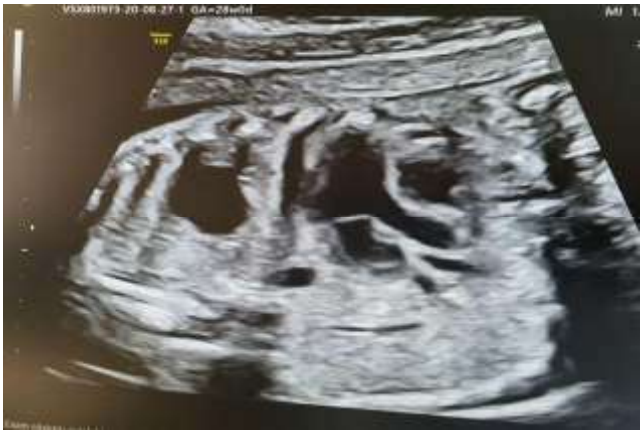

Figure 6 **Aortic arch view.**

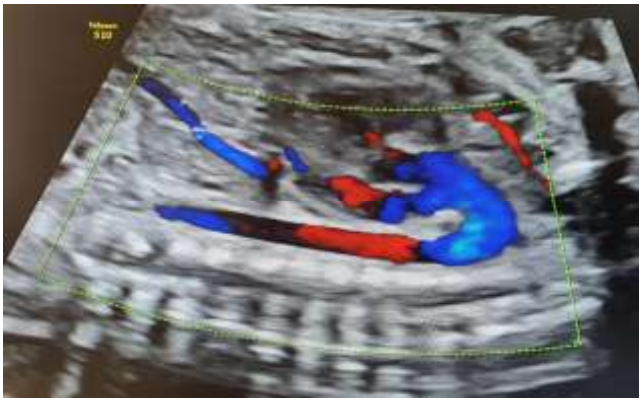

Figure 7 **Aortic arch view - Color Doppler.**

CONCLUSION

CHDs are the most common congenital anomalies. It is essential to mention the need for collaboration between perinatologists, pediatric cardiologists, and pediatric cardiac surgeons in order to make final decision on the treatment of a fetus with CHD.

In the field of fetal echocardiography, there is always a need for further and better staff training as well as the application of new software technologies in ultrasound diagnostics, in order to detect CHD as early as possible and to provide better treatment to the affected patients.

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Case report on sentinel lymph node in contralateral axilla at ipsilateral breast tumor recurrence

Prikaz slučaja sentinel limfnog čvora u kontralateralnoj aksili kod recidivnog tumora ipsilateralne dojke

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ABSTRACT

In modern approach of treating breast cancer, a method of choice is represented by sentinel (SLN) biopsy of axillary lymph node. The method is based on the fact that lymphatic current bears malignant cells in linear flow, thus if the first (sentinel) lymph node is not malignantly infiltrated, there is a huge possibility that the same fact is valid also for the lymph nodes being placed behind sentinel. The aim of this case report is to point out the influence of previously performed surgical treatment and irradiation to forming new pathways of lymphatic drainage. In our case, a patient born in 1965 was surgically treated in 1995 for the right breast carcinoma. Applied surgical method comprised of conserving surgery with dissection of unilateral axillary lymph nodes. Irradiation was performed postoperatively. In December 2018, mammography confirmed a tumor mass, size 30x18 mm, with infiltration and retraction of the skin and right breast nipple. The mass was patho-histologically verified as ductal carcinoma (NST), G3, ER and PR negative, HER/neu negative. Surgical procedure was indicated with SLN biopsy of the right breast. Upon the performed procedure, sentinel lymph node appeared in the front axillary line on the left (contralateral), followed by the second one just behind it, caused by damaged lymph drainage on the right. After 25 minutes, the lymph node was observed in the right axilla, showing significantly less intensity. Afterwards, the patient was subjected to a surgery when radical surgical procedure was performed on the right, and SLN biopsy of the left axilla and biopsy of retro-areolar area of the left breast. In the current practice related to this method, it was the first time that we had the case of the sentinel lymph node presence in the contralateral axilla. This case report may serve as an illustration of the possibilities of lymphatic spreading of disease following the primary drainage spot dissection, thus, imposing lymphoscintigraphy as a method of choice for patients being previously surgically treated or irradiated.

Key words: breast cancer, ipsilateral tumor recurrence, sentinel lymph node, lymphoscintigraphy, contralateral axilla

SAŽETAK

U savremenom pristupu tretiranja karcinoma dojke metodu izbora predstavlja sentinel biopsija aksilarnog limfnog čvora. Metoda se zasniva na činjenici da limfna struja nosi maligne ćelije linearnim tokom, te da ukoliko prvi (stražarski) limfni čvor nije maligno infiltriran, postoji velika vjerovatnoća da isto vrijedi i za limfne čvorove koji se nalaze iza stražarskog. Cilj ovog prikaza slučaja je staviti naglasak na uticaj prethodno učinjenog operativnog zahvata, kao i zračenja na stvaranje novih puteva limfne drenaže. U slučaju kojeg predstavljamo pacijentica 1965. godište je operativno tretirana zbog karcinoma desne dojke 1995. godine, kada se učini poštedni operativni zahvat sa disekcijom istostranih pazušnih limfonoda. Postoperativno provedena iradijacija. U decembru 2018. godine pacijentici se radiološki utvrdi neoplastična promjena veličine 30x18 mm sa infiltracijom i retrakcijom kože i mamile desne dojke. Promjena se patohistološki verificira kao duktalni karcinom (NST), G3, ER i PR negativna, HER2/neu negativan. Pacijentici indiciran operativni zahvat sa SLN biopsijom desne dojke. Po sprovedenoj proceduri, zbog narušene limfne drenaže desno, stražarski se limfni čvor prikaže u prednjoj aksilarnoj liniji lijevo, a zatim i drugi neposredno iza njega. Nakon 25 minuta uslijedi i prikaz limfnog čvora u desnoj aksilarnoj jami, puno slabijim intenzitetom. Pacijentica se potom podvrgne operativnom zahvatu kada se učini radikalni operativni zahvat desno, kao i SLN biopsija lijeve aksile, te biopsija retroareolarnog područja lijeve dojke. U dosadašnjoj praksi sa ovom metodom, po prvi put smo se susreli sa slučajem prikaza stražarskog limfnog čvora u kontralateralnoj pazušnoj jami. Ovaj prikaz slučaja može ilustrovati mogućnosti limfatičnog širenja bolesti po učinjenoj disekciji primarnog mjestalimfne drenaže, što nameće limfoscintigrafiju kao metodu izbora kod pacijenata koji su prethodno operativno tretirani ili iradirani.

Ključne riječi: rak dojke, ipsilateralni recidiv, sentinel limfni čvor, limfoscintigrafija, kontralateralna aksila

INTRODUCTION

Sentinel lymph node or the guardian node is being defined as the first lymph node or a group of nodes in which the spreading of cancer cells will start. Spreading of some forms of cancer usually has common progress, spreading at first into first regional lymph nodes, then into the next group of lymph nodes and so on, since the lymph flow is directed. The main basin of the lymphatic drainage flow from the breast is ipsilateral axilla (1).

The concept of surgery and biopsy of sentinel lymph node is to show whether cancer cells spread on the first drainage lymph node or not. If there are no cancer cells in sentinel lymph node, there are great chances that carcinoma has not spread to other parts of body as well. It is known that sentinel lymph node appears even in extra-axillary areas in the cases of ipsilateral breast cancer recurrence caused by damage of lymphatic drainage pathways, which is a consequence of previously performed treatment, for example surgery of axilla or irradiation of breast (2).

Prior to surgical treatment, detection of SLN by nuclear-medical diagnostics is performed. Namely, in intra-dermal or peri-tumoral manner, the patient was injected by Technetium marked Nano-colloid, upon which, gamma camera visualized SLN and which was marked with Cobalt sources (Co57).

Biopsy of sentinel lymph node is performed in the manner to inject radioactive technetium or blue dye, or both of them, in the vicinity of tumor in order to localize sentinel lymph node. By applying nuclear-medical diagnostic agent Tc-99m, it is possible to identify sentinel lymph node in even 99% of breast cancer patients, but by applying both techniques it is possible to identify sentinel lymph node in all patients (3).

Injecting dye or radioactive technetium is performed either peri-tumoral at palpable lesions, while at non-palpable lesions it is recommended to use ultrasound or roentgen while injecting. About 0.2 to 0.5 ml of dye or 5-10 MBq marked colloidal particles of radioactive technetiumIt is injected. Sentinel lymph node is then identified either by dye, either by using gamma probe. Surgeon then makes a small skin incision above lymph node and removes it.

Afterwards, the sentinel lymph node is sent to patho-histology analysis. Depending on the results of patho-histology analysis, the surgeon may decide whether to promptly remove axillary lymph nodes or not.

AIM

The aim of this case report was to point out the influence of previously performed surgical treatment and irradiation to forming new pathways of lymphatic drainage.

CASE REPORT

A 53 years old patient contacted her attending doctor due to the retraction of the right nipple followed by the pain in the same. She was surgically treated in 1995 due to verified right breast cancer, when conserving surgery was performed with dissection of unilateral axillary lymph nodes. She was post-operatively irradiated and was under regular radiologic control.

In December 2018, the patient was diagnosed with ipsilateral breast tumor recurrence, 30 x 18 mm in size (Figure 1 and 2), with infiltration and retraction of skin and nipple and retro-areal tumor mass located on the left breast with benign characteristics. The change in the right breast was patho-histological verified as ductal carcinoma (NST), G3. Estrogen, progesterone and HER2 were negative. Physical checkup of right breast was in correlation with diagnostics while findings on the left breast did not show presence of any malignancy.

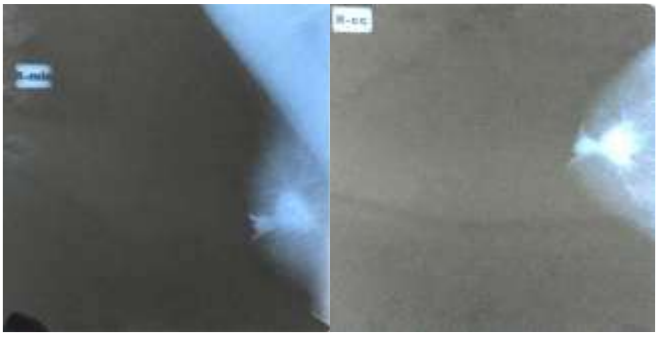

Figure 1 and 2 **Mammography of the right breast (ML and CC projection)**.

The case was presented at the Oncology Concilium for Breast Diseases where surgery with SLN biopsy was indicated. Preoperatively, the patient went through lymph o-scintigraphy during which, three doses of Nano-colloid in the volume of 0.4 ml per dosage were applied into the right breast. Lymphatic drainage pattern was disturbed thus the first drainage lymph node appeared in the front left axillary region and immediately after another one beneath the first. After 25 minutes, drainage lymph node appeared in the right axillary region, significantly less intense. They were marked with Co57 source and their localization was checked by gamma probe followed by cutaneous marking (Figure 3).

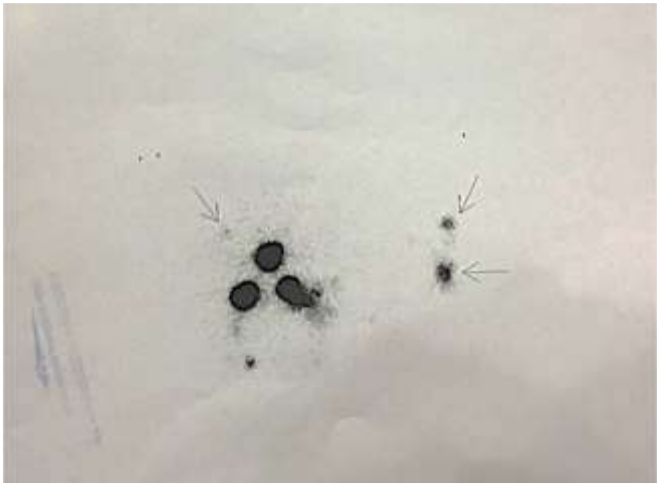

Figure 3 **Preoperative lymphoscintigraphy (arrows showing sentinel lymph nodes and the intensity of the signal).**

The patient went through surgery including radical surgical treatment on the right, and also sentinels biopsy of the left axilla and biopsy of the left breast retro-areolar area.

Intraoperative biopsy of the axillary lymph node from the left axilla revealed by gamma probe, did not show the existence of metastasis. Intraoperative biopsy of suspected tumor mass in the left breast indicated benign fibrocystic changes and papillomatosis.

DISCUSSION

Application of sentinel method showed contralateral lymph node thus completely changed the algorithm of the patient's treatment meaning that positivity of the lymph node in the left axilla warranted surgical team to remove the same and perform intraoperative analysis and also the suspected change in the left breast.

A positive contralateral axillary lymph node is considered distant metastasis (M1). However, if asymptomatic metastasis is discovered after examining the SLN microscopically then it is considered primary node staged as pN1 (4).

In patients with the previous breast or axilla surgical treatment, or irradiation in quoted areas, alteration of lymphatic drainage pathways is expected. Those new pathways understand lymph nodes along with internal mammary artery, internal mammary, sub or supra-scapular lymph node, and very rarely contralateral lymph nodes, as was the case in our report (1).

Paradoxically in patients with altered or disrupted lymphatic drainage pathways this may be the strongest argument for reoperative SLNB (6).

Lymphoscintigraphy is the only method that may successfully reveal extra-axillar places of malignant disease spreading, and as such, has great influence to curing algorithm of each patient (5). In the case of positive SLN biopsy of contralateral lymph node, the same will influence surgical algorithm. In such circumstances the surgeon would be forced to perform dissection of contralateral axilla which would not be possible without lymphoscintigraphy and these metastases would be overlooked. (7) In such manner, it becomes very useful tool in treating patients with breast cancer recurrence.

Positivity of contralateral axilla would then contribute to earlier detection of metastasis thus leading to more efficient cure of the patient.

Given that the SLN biopsy showed absence of malignant cells, as in our case, and axillary dissection was not performed, patients were exposed to lower pain, lack of sensation and better mobility of upper extremities (1).

CONCLUSION

Contemporary approach to treatment of cancer understands the use of sentinel biopsy. We would like to emphasize the disturbance of lymph drainage pathways after performed surgical treatment. This case report may serve as an illustration of the possibilities of lymphatic spreading of disease following the primary drainage spot dissection, thus, imposing lymphoscintigraphy as a method of choice for patients being previously surgically treated or irradiated.

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Atypical posterior reversible encephalopathy syndrome (PRES) in a young female patient: case report

Atipični sindrom posteriorne reverzibilne encefalopatije (PRES) kod mlade pacijentice: prikaz slučaja

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ABSTRACT

Introduction: posterior reversible encephalopathy syndrome (PRES) is a rare neuroradiological entity most often presented with headache, epileptic seizures, altered consciousness, nausea, vomiting and visual loss. If recognized and treated early, PRES syndrome most often resolve causing no sequels. Aim: to present a case of atypical press syndrome in a young female patient with poor neurological outcome. Case report: a 34-year old young female patient was admitted to our Neurological department with a 2 month history of vertiginous symptoms. 10 years ago, she suffered from deep vein thrombosis, otherwise she was healthy. On her sixth day of hospitalization, she reported a strong headache with vomiting, hypertension crisis was registered (BP 180/100 mm Hg) followed by alteration of consciousness. A head magnetic resonance imaging (MRI) showed signs of atypical PRES with altered signal intensity and diffusion restriction bilaterally occipital, and in the area of the splenium corpus callosum sagittal and slightly left. A patient developed a disartric speach and left side weakness. The folow-up MRI showed vascular ischemic lesions, and on MRA sequences, the left posterior inferior cerebellar artery (PICA) was not displayed. Her diagnostic work-up did not reveal any pathological findings and patient was discharged after 20 days, with left-side hemiparesis and disartric speech (NIH Stroke Scale 7). Conclusion: most often, the clinical outcome of PRES is favorable, however, atypical presentations have been observed. PRES should be considered as a serious condition that requires urgent and prompt evaluation in order to provide the best clinical management for patients.

Key words: posterior reversible encephalopathy, magnetic resonance imaging, contrast enhancement

SAŽETAK

Uvod: sindrom posteriorne reverzibilne encefalopatije (PRES) predstavlja rijedak neuroradiološki entitet koji se najčešće prezentuje glavoboljom, epileptičnim napadima, promijenjenom sviješću, mučninom, povraćanjem i gubitkom vida. Ako se prepozna i liječi rano, PRES sindrom se najčešće povuče bez posljedica. Cilj: prikazati slučaj atipičnog PRES sindroma kod mlade pacijentice sa lošim neurološkim ishodom. Prikaz slučaja: 34-godišnja mlada pacijentica primljena je na Neurološki odjel s dvomjesečnom anamnezom simptoma vrtoglavice. Prije 10 godina prebolovala je duboku vensku trombozu, inače je bila zdrava. Šesti dan hospitalizacije prijavila je jaku glavobolju s povraćanjem, registrirana je hipertenzijska kriza (BP 180/100 mm Hg), praćena poremećajem svijesti. MRI glave pokazao je znakove atipičnog PRES-a s izmijenjenim intenzitetom signala i restrikcijom difuzije, obostrano okcipitalno, u području splenium korups kalozuma i blago lijevo. Pacijentica je razvila disartričan govor i slabost lijeve strane tijela. Kontrolni MRI pokazao je vaskularne ishemijske lezije, dok na MRA sekvencama lijeva PICA nije prikazana. Njena dijagnostička obrada nije otkrila nikakve patološke nalaze pa je pacijentica otpuštena nakon 20 dana s lijevom cerebralnom hemiparezom i disartričnim govorom (NIHSS 7). Zaključak: klinički ishod PRES-a je najčešće povoljan, ali opažene su i atipične prezentacije. PRES treba shvatiti kao ozbiljno stanje koje zahtijeva hitnu i brzu procjenu kako bi se našim pacijentima pružio najbolji klinički tretman.

Ključne riječi: posteriorna reverzibilna encefalopatija, MRI, podizanje signala

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) represents a rare neuroradiological entity that can pose a real diagnostic difficulties. The proposed pathophysiological mechanisms include cerebral vasoconstriction causing subsequent infarcts in the brain, impaired cerebral autoregulation with consequent development of vasogenic edema, and endothelial dysfunction with disruption of blood-brain barrier integrity (1).

Most often described symptoms include headache, epileptic seizures, altered consciousness, nausea, vomiting and visual loss (2). It is often associated with other medical conditions, among them, most often with hypertension, eclampsia and preeclampsia, severe hypercalcemia, renal failure and autoimmune diseases (2,3).

Characteristic neuroradiological presentation of PRES includes hyperintensity on fluid-attenuated inversion recovery (FLAIR) images in the parietooccipital and posterior frontal cortical and subcortical white matter; less commonly, the brainstem, basal ganglia, and cerebellum are involved (4). Atypical imaging features include contrast enhancement, hemorrhage, and restricted diffusion on magnetic resonance imaging (MRI) (5,6).

If recognized and treated early, PRES syndrome most often resolve causing no sequels. However, clinical presentations with poor outcome have been described.

AIM

The aim of our study was to present a case of atypical press syndrome in a young female patient with poor neurological outcome.

CASE REPORT

A 34-year old female patient was admitted to Neurology Clinic of the Clinical Center University of Sarajevo in September 2018 with a 2 month history of vertiginous symptoms. She was a smoker, and consumed alcohol rarely, no registered hypertension, married without children, no registered pregnancy losses. Ten years ago, she suffered from deep vein thrombosis, well recovered and now without chronic use of medications. No other significant medical history was reported. Her neurological exam was unremarkable by admission.

On her sixth day of hospitalization, she reported a strong headache with vomiting. Hypertension crisis was registered (BP 180/100 mm Hg) followed by alteration of consciousness. Her laboratory examination did not reveal any abnormalities, liver and renal tests were normal. Pregnancy test was negative. Cerebrospinal fluid protein levels were slightly elevated with normal cell counts. Electroencephalography showed bilateral temporal - occipital slowing. A head MRI (Figure 1a and 1b) showed the existence of a zone with altered signal intensity and diffusion restriction bilaterally occipital, and in the area of the splenium corpus callosum sagittal and slightly left. Based on their MR characteristics, it was possible that these were lesions of vascular etiology with hypoxic microischemic characteristics, all possible in the field of atypical forms of PRES.

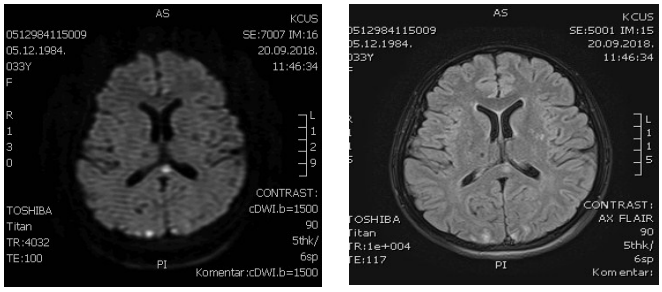

Figure 1a and 1b **Brain MRI (DWI and Flair) showed the existence of a zone with altered signal intensity and diffusion restriction bilaterally occipital, and in the area of the splenium corpus callosum sagittal and slightly left.**

The patient was admitted to intensive care unit where two episodes of generalized tonic-clonic epileptic attacks were registered. She was threated with intravenous fluids, antiepileptics and antihypertensive medications with contionous monitoring for haemodynamic stability. She recovered on the plane of the consciousness, but her neurological exam discovered disartric speech and proportional left-side weakness (NIHSS 9). A folow up MRI showed infratentorially bilaterally, in the vermis and in the middle cerebral penduncle on the left, extensive zones of hypersignals on T2 FSE and T2 FLAIR, hyposignals on T1, showed diffusion restriction in places, especially in the area of middle cerebral penduncle in terms of vascular ischemic lesion, more recent date - subacute phase. Postcontrast in this area there was increase in signal intensity, especially in the area of the left cerebellar hemisphere, most likely in terms of luxury perfusion. Supratentorially, the thalamic right zone of similar MR characteristics that partially showed diffusion restriction and in some places raises the signal intensity postcontrast (luxury perfusion), corresponded to lacunar infarction in the subacute phase. Parietooccital bilaterally subcortically visible was previously verified part of the confluent zone without diffusion restriction, corresponded to vascular ischemic lesions, of older date, with postcontrast luxury perfusion especially cortical (Figure 2a-d).

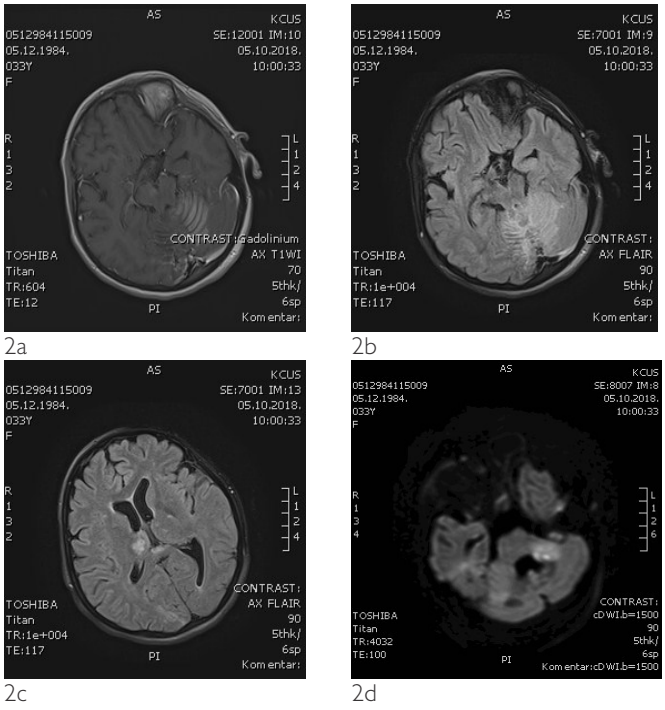

Figure 2 **Brain MRI (T1, T2 FLAIR, DWI).**

Figure 2.a-d. Brain MRI (T1, T2 FLAIR, DWI) showing infratentorially bilaterally, in the vermis and in the middle cerebral penduncle on the left, extensive zones of hypersignals on T2 FSE and T2 FLAIR, hyposignals on T1, show diffusion restriction in places, especially in the area of middle cerebral penduncle in terms of vascular ischemic lesion, more recent date - subacute phase. Postcontrast in this area there was increase in signal intensity, especially in the area of the left cerebellar hemisphere, most likely in terms of luxury perfusion. Supratentorially, the thalamic right zone of similar MR characteristics that partially shows diffusion restriction and in some places raises the signal intensity postcontrast (luxury perfusion), corresponded to lacunar infarction in the subacute phase. Parietooccital bilaterally subcortically visible are previously verified part of the confluent zone without diffusion restriction, corresponded to vascular ischemic lesions, of older date, with postcontrast luxury perfusion especially cortical.

On MRA sequences, the left PICA was not displayed, the other blood vessels of the Willis circle were unremarkable, with no MR signs of aneurysmal dilatations and/or AVM (Figure 3).

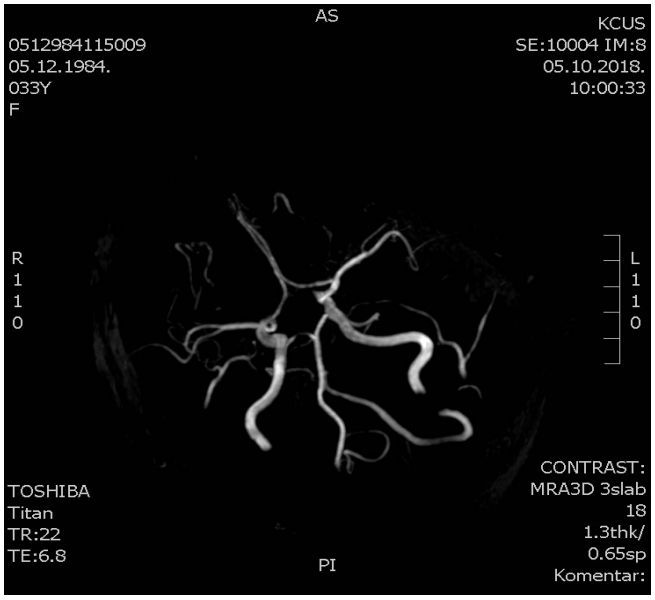

Figure 3MRA 3D showing the left PICA was not displayed

At the time, she was re-admitted to the neurological ward; an extensive diagnostic evaluation we performed including serologic and immunologic tests, testing for antiphospholipid antibodies, and hereditary thrombophilia, cardiovascular work-up including holter electrocardiogram (EKG) and echocardiography, Color Duplex, with no pathological findings observed. She was treated with antithrombotic therapy with statins, and physical therapy was included. She was discharged after 20 days, with left-side hemiparesis and dysarthric speech (NIH Stroke Scale 7).

DISCUSSION

Posterior reversible encephalopathy syndrome (PRES) was first described more than 20 years ago, in 1996 (7). From that time, a great progress has been made in its evaluation, mostly due to uprising attainability of highly sophisticated neuroimaging methods. It is generally considered to be a benign condition, if medical treatment is applied promptly. However, cases with fatal outcome have been described (8,9).

Chen, et al. performed a meta-analysis investigating the risk factors associated with bad prognosis of PRES (10). According to their findings, the presence of hemorrhage or cytotoxic edema could be a predictor of potentialy fatal clinical outcome (10). Other authors report severe encephalopathy, hyperglycemia, presence of neoplastic disease, extendeed time in treating the trigger, the presence of multiple comorbidities, elevation of CRP, low CSF glucose, and presence of coagulopathy to be associated with higher mortality (11-14).

In our case report, development of PRES was associated with hypertension crysis. Sudden elevation of blood pressure have been recognised as a provoking mechanism for developing PRES (15).

Other authors also reported a high blood presurre in presence of PRESS, indicating that these two condition could be conditioned. Moreover, a common pathophysiological mechanism has been proposed (10).

Carefull reducing levels of blood pressure is thought to make a full recovery of 90% of the patients (16). However, irreversible clinical presentations of PRESS have been described, causing a severe neurological deficit or even a death in up to 20% of the patiens (14,17).

Our young patient developed an ischemic stroke, which was described as a rare complication of PRES syndrome (15). Chinese authors reported a case of PRES complicated with ischemic stroke located in brainstem, in, previously healthy, 36 years old female (18). Imataki, et al. describe a case of PRES leading to the development of cerebrovascular incident after use of imunosupressive drug (19).

We performed a substantial search for underlaying coagulopathy in our patient, mostly due to data of suffered deep vein trombosis in her prevoius medical hystory. However, none of our findigs could explain development of ischemic stroke in this young person.

Previous research implicate the association between diffusion restriction and piteous clinical result of PRES (10). Stereotypical PRES lesions do not show restricted diffusion and Covarrubias et al. proposed that diffusion restriction may be the inital sign of irreversible lesions (20).

However, there are studies where no significant association was found (12). Moreover, complete resoluti on of diffusion restriction was observed during follow-up (21). Our case report showed that diffusion restriction was associated with adverse outcome in our patient with PRES. Additionaly DWM involvement was more often described in patiens with PRESS assosiated with hypertension, as was presented in our case (21).

Nevertheless, cases in completely normotensive patients have been described (22).

CONCLUSION

Despite that, most often, the clinical outcome of PRES is favorable, atypical presentations have been observed. PRES should be considered as a serious condition that requires urgent and prompt evaluation in order to provide the best clinical management for patients.

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Neuroendocrine carcinoma (NEC) of gallbladder - a case report

Neuroendokrini karcinom žučne kese (NEC) - prikaz slučaja

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ABSTRACT

Introduction: neuroendocrine carcinomas (NEC) of the gallbladder are very rare malignant tumors, accounting for less than 1% of all tumors. For advanced NEC gallbladder prognosis is usually poor, but better outcomes can be obtained with aggressive radical surgery and chemotherapy. Unfortunately, there is no standard therapeutic strategy for several reasons, including disease rarity, lack of prognostic factors, inability to recognize progression, and limited understanding of lesion biology. Aim: to report an incidental finding of NEC obtained after pathohistological analysis of the gallbladder removed for clinical and radiological signs of acute calculous cholecystitis. Case report: a 74-year-old patient was admitted to Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo as an emergency due to clinical, radiological and laboratory signs of acute cholecystitis. An indication is given for immediate surgical treatment, which was performed on the day of admission. The operation began with a laparoscopic approach, and due to the complexity of the findings and the impossibility of displaying the elements of the Calot's triangle, a conversion was performed, and the gallbladder was removed with the classic subcostal approach. The postoperative course was as expected, and the patient was discharged from the hospital on the sixth postoperative day. Pathohistological findings supported neuroendocrine gallbladder cancer (NEC), grade III, pT1N1MxRo. The Oncology counciliatory team indicated chemotherapy, but we found out that the patient never contacted the Oncologist to begin the treatment. Conclusion: by presenting this case, we want to emphasize to physicians of all levels of health care the severity of symptoms of pain in the area of the upper right quadrant of the abdomen. Any ultrasound-verified thickenings or polypoid formations of the gallbladder deserve special supervision, especially in elderly women.

Key words: gallbladder, carcinoma, treatment, surgical procedures

SAŽETAK

Uvod: neuroendokrini karcinomi žučne kese (NEC) su vrlo rijetki maligni tumori, koji čine manje od 1% svih tumora. Za uznapredovale NEC žučne kese prognoza je obično loša, ali se bolji ishodi mogu dobiti agresivnom radikalnom operativnom i kemoterapijom. Nažalost ne postoji standardna terapijska strategija iz više razloga, uključujući rijetkost bolesti, nedostatak prognostičkih faktora, nemogućnost prepoznavanja progresije i ograničeno razumijevanje biologije lezije (2). Cilj: izvjestiti o slučajnom nalazu NEC-a dobivenom nakon patohistološke analize žučne kese izvađene zbog kliničkih i radioloških znakova akutnog kalkuloznog holecistitisa. Prikaz slučaja: pacijentica starosti 74 godine primljena u hitnom prijemu na Kliniku za opštu i abdominalnu hirurgiju Kliničkog centra Univerziteta u Sarajevu zbog kliničkih, radioloških i laboratorijskih znakova akutnog holecistitisa. Postavi se indikacija za neodložan hirurški tretman koji se učini po danu prijema. Operacija otpočne laparoskopskim pristupom, da bi se zbog složenosti nalaza i nemogućnosti prikazivanja elemenata Calotovog trougla učinila konverzija, a žučna kesa izvadila klasičnim subkostalnim pristupom. Postoperativni tok se odvija očekivano, a pacijentica se šesti postoperativni dan otpušta kući. Patohistološki nalaz govori u prilog neuroendokrinog karcinoma žučne kese (NEC), gradusa III, pT1N1MxRo. Onkološki konzilij za maligne bolesti digestivnog trakta indicira nastavak liječenja kemoterapijom, no kako saznajemo, pacijentica se nikada nije javila onkologu radi započinjanja tretmana. Zaključak: ovim radom želimo skrenuti pažnju ljekarima svih nivoa zdravstvene zaštite na ozbiljnost simptoma bolnosti u predjelu GDK-a. Poseban nadzor zaslužuju bilo kakva UZ verificirana zadebljanja ili polipoidne tvorbe žučnog mjehura, a osobito kod starijih osoba ženskog spola.

Ključne riječi: žučna kesa, karcinom, tretman, hirurške procedure

INTRODUCTION

Neuroendocrine gallbladder carcinomas (NECs) are very rare malignant tumors, accounting for less than 1% of all tumors. Most neuroendocrine cancers are found in the gastrointestinal tract (66%) and respiratory tract (31%). In the gastrointestinal tract, neuroendocrine carcinomas are usually localized in the rectum, jejunum, ileum, and pancreas. NEC of the gallbladder and common

bile duct occurs in 2.2% of all neuroendocrine cancers, and the knowledge about it is based on individual cases (1,2).

The World Health Organization (WHO), according to the current classification from 2010, neuroendocrine tumors (NET) include well-differentiated NET (classic carcinoid tumors), well-differentiated NEC (atypical carcinoids or malignant carcinoids), poorly differentiated NEC (high-grade carcinoma, small / large cell), and mixed exocrine-endocrine carcinomas. The most common neuroendocrine gallbladder tumors are classical NEC and highly malignant small cell NEC (3).

The prognosis of NEC gallbladder is usually poor, but better outcomes can be obtained with aggressive radical surgery and chemotherapy (4). Unfortunately, there is no standard therapeutic strategy for several reasons, including disease rarity, lack of prognostic factors, inability to recognize progression, and limited understanding of lesion biology (4). The most common metastatic sites of NEC gallbladder are lymph nodes (88%), liver (88%), lungs (23%) and peritoneum (19%) (4).

AIM

To report an incidental finding of NEC obtained after pathohistological analysis of the gallbladder removed for clinical and radiological signs of acute calculous cholecystitis.

CASE REPORT

A 74-year-old patient was examined by an abdominal surgeon due to intense pain below the right costal arch, followed by vomiting. She stated that the problems had been going on for a long time, her skin did not turn yellow and she did not lose weight. Her appetite was slightly weakened in the last two weeks. She was using the therapy for hypertension. She denied having other chronic diseases, surgeries and injuries. Also, the patient denied food and drug allergies. Clinical examination verified palpatory pain of the right upper quadrant and epigastrium.

An indication for urgent surgical treatment was set. The operation started with a laparoscopic approach, and after the exploration and the impossibility of showing Calot's triangle, a conversion was made, and the gallbladder was removed with the classic approach. During the operation, the patient was stable and was postoperatively placed at the hospital ward.

On the first postoperative day, the laboratory parameters were in reference values. The patient was treated with antibiotics, analgesics, low molecular weight heparin, IPP, and analgesics. The placed abdominal drain was removed on the third postoperative day. The bowel passage was established spontaneously, and on the sixth postoperative day the patient was discharged from the hospital.

Pathohistological diagnosis verified neuroendocrine gallbladder cancer (NEC), grade III, pT1N1MxRo. The gallbladder was 113 mm long and 1-6 mm thick. There were 41 pathological mitoses in 10 large visual fields. Immunoprofile: Cytokeratin ++, Leukocyte Common Antigen -; S-100 protein -, Vimentin-Synaptophysin +++; Chromogranin A ++; Neutral-Cell Adhesion Molecule CD 56 +++; Thyroid transcription factor-1 (TTF1) -; Caudal-related homebox gene 2 (CDX2) +; Proliferative index Ki67 + in about 70% of cells. Numerous calculi (largest 16mm) were found in the lumen. Along the neck of the gallbladder metastatically positive lymph node with dimensions 23x17x13mm.

The patient was referred to the Oncology counciliatory team which indicated further treatment with chemotherapy.

The patient was informed of the opinion Oncology counciliatory team, but never contacted the Oncologist to begin the treatment.

In collaboration with the attending family medicine physician, we found out that the patient was alive nine months after the operation and was currently undergoing physical therapy for osteoporosis.

DISCUSSION

Neuroendocrine cancers of the gallbladder (GB-NEC) have a higher incidence in women aged 35 to 80 years. The study by Ahn, et al. found that a smaller number of functional GB-NECs had specific presentations (5). Moreover, according to previous studies, most were not functional and the clinical signs of GB-NEC were not specific (6,7). Our patient had a nonsecretory tumor, with no clinical signs related to secreted neuropeptides or any specific characteristics.

Matsuo, et al. suggest that radiological, pathological, and immunohistochemical diagnosis are necessary for accurate preoperative diagnosis (6). Radiological diagnostics, such as CT, MRI, ultrasound, and tumor biomarkers, usually do not help to suspect NEC of the gallbladder. Most NECs are identified incidentally during routine histological examination of the gallbladder after surgical extraction and are often accompanied by cholelithiasis and cholecystitis. In our case, the patient was admitted with clinical and radiological signs of acute calculous cholecystitis, and an indication for immediate surgical treatment in terms of cholecystectomy was set. Neuroendocrine carcinomas are highly malignant tumors that progress rapidly, resulting in early liver invasion and lymphatic metastases. In our case, it was a tumor that did not penetrate the gallbladder wall or other adjacent structure (T1), but the cancer cells were found in the lymph node of the gallbladder neck (N1), which coincides with the data in the literature in favour of early lymphatic invasion. No other pathological substrate (M0) was found by laparoscopic exploration, and the American Cancer Society defines our case as stage IIIb (8).

Literature data suggest that the formation of the gallbladder NETs supports the presence of metaplasia in the gallbladder caused by chronic irritation caused by cholecystitis. Our patient had a history of long-term chronic cholecystitis.

The therapy of choice for NEC gallbladder is cholecystectomy. In surgical treatment, a variety of surgical procedures can be performed ranging from simple cholecystectomy to extensive radical resection (including local lymph node removal and metastatic resection) (9). While simple cholecystectomy is indicated for preinvasive and early detection cancers (In situ, T1), more aggressive in the form of radical cholecystectomy and regional lymphadenectomy in combination with liver resection is performed in advanced lesions (9).

Since in our case there was no postoperative suspicion of NEC, and the diagnosis was made postoperatively, urgent cholecystectomy with pathohistologically clear resection margin and extripation of available lymph node, was performed as surgical therapy of choice.

In a study of the MSKCC (Memorial Sloan-Kettering Cancer Center), which included 13 patients with gallbladder NEC, the median survival was 9.8 months, which did not differ significantly from the mean survival of patients (n = 435) with gallbladder adenocarcinoma, which was 10.3 months (10). A study by Fujii, et al. showed a poor survival rate of 28% and 0% at the end of the first and second year postoperatively, in a respective study involving 53 patients with small cell carcinoma of the bile duct. These findings suggest a poorer prognosis for GB-NEC compared with gallbladder

adenocarcinoma, probably due to a higher percentage of patients in the advanced stage of the disease and with lymphatic metastases at the time of diagnosis. In the ninth month, following the surgery we obtained information that the patient was alive, in good general condition, which coincided with the data in the available medical literature.

Data on the prognosis of GB-NEC disease is relatively limited. According to previous studies, a significant advantage in five-year survival rates was observed in patients with T1-2 stage who underwent radical surgery compared to those who underwent only standard cholecystectomy (38% -100% vs. 17% -65%) (11). Our patient underwent standard cholecystectomy in the emergency program. Unfortunately, the patient refused further treatment, but judging by the data from the literature, given the stage of T1 tumor, we would predict a favourable prognostic outcome in case she accepted further treatment.

Research on GB-NEC suggests that adjuvant radiotherapy and chemotherapy may be useful in patients with this malignancy (12).

Due to the small number of reported cases of NEC, to date, standard protocols for chemoradiotherapy of this tumor have not been proposed. Through an unofficial consultation with an oncologist for malignant diseases of the digestive tract, we have learnt that patients who treated with chemotherapeutics due to GB-NEC in our institution have shown satisfactory treatment results.

Unfortunately, our patient did not contact the oncologist for the continuation of therapy, and judging by the data from the medical literature, the expected probability of survival for the presented case is not more than two years.

CONCLUSION

In this study, we wanted to draw attention of all levels of health care physicians to the severity of pain symptoms in the area of the upper right quadrant of the abdomen. Any ultrasound-verified thickenings or polypoid formations of the gallbladder deserve special supervision, especially in elderly female. Timely diagnosis and surgical treatment for cholelithiasis, which can mask the presence of tumors, is imperative in reducing the incidence of detecting malignancy at an advanced stage.

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