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CONTENTS

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
Novi Sad *Vase Stajića 9* *Srbija*

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DETERMINATION OF DENTOALVEOLAR PARAMETERS IN PATIENTS WITH PROGENIA

UTVRĐIVANJE DENTOALVEOLARNIH PARAMETARA KOD PACIJENATA SA PROGENIM ZAGRIŽAJEM

Nataša PUŠKAR, Milica PUŠKAR, Predrag VUČINIĆ, Stojan IVIĆ and Đorđe PETROVIĆ

Summary

Introduction. Class III malocclusions are characterized by a more prominent lower jaw compared to the upper jaw and a Class III skeletal and dentoalveolar relationship according to Angle. In the scientific literature, there is a small amount of data on the morphological characteristics of malocclusion in different populations, so there is a justified need to examine the morphological characteristics of Class III malocclusion in the population of Vojvodina. The aim of this study was to determine the morphological characteristics of Class III malocclusions, to compare them with the average values found in the scientific literature, and to determine the correlation between the examined parameters of the upper and lower jaw. **Material and Methods.** This retrospective study included subjects with Class III dentoalveolar malocclusion treated at the Dentistry Clinic of Vojvodina in Novi Sad. The method of random selection was used to select 50 study models. The data were statistically processed with a significance level of $p < 0.05$. **Results.** The obtained results indicate that the sum of crown width of the mandibular incisors, the length of the mandibular dental arch, and the mandibular apical base in subjects with Class III malocclusion are higher than the average values in the general population. The values of the posterior width of the maxillary dental arch in the examined group are lower compared to the average values in the general population. **Conclusion.** Subjects with Class III malocclusion present with a greater mandibular dental arch in regard to the maxillary dental arch.

Key words: Malocclusion; Prognathism; Malocclusion, Angle Class III; Cephalometry; Incisor; Dental Arch

Sažetak

Uvod. Malokluzije III klase karakteriše razvijenija donja vilica u odnosu na gornju i skeletni i dentoalveolarni odnos III klase po Englu. U naučnoj literaturi postoji mali broj podataka o morfološkim karakteristikama malokluzija u različitim populacijama, pa zato postoji opravdana potreba za ispitivanjem morfoloških karakteristika kod malokluzije III klase u vojvođanskoj populaciji. Cilj rada bio je da se utvrde morfološke karakteristrike malokluzija III klase; da se one uporede sa prosečnim vrednostima u populaciji koje su dobijene iz naučne literature i da se utvrdi korelacija između ispitivanih parametara u gornjoj i donjoj vilici. **Materijal i metode.** Istraživanje je sprovedeno kao retrospektivna studija na studijskim modelima ispitanika koji imaju dentoalveolarnu malokluziju III klase, a koji su lečeni na Klinici za stomatologiju Vojvodine u Novom Sadu. Metodom slučajnog izbora odabrano je 50 studijskih modela. Podaci su statistički obrađeni sa nivoom značajnosti $p < 0,05$. **Rezultati.** Dobijeni rezultati ukazuju na to da je suma širine krunica donjih inciziva, dužina mandibularnog zubnog luka i mandibularne apikalne baze kod ispitanika sa malokluzijom III klase veća od prosečnih vrednosti u populaciji. Vrednosti zadnje širine gornjeg zubnog luka u ispitivanoj grupi su manje u odnosu na prosečne vrednosti u populaciji. **Zaključak.** Ispitanici sa malokluzijom III klase imaju veću razvijenost donjeg, a manju razvijenost gornjeg zubnog luka.

Ključne reči: malokluzija; progenija; malokluzija III klase po Englu; cefalometrija; incizor; zubni luk

Introduction

The main characteristic of true prognathism is mandibular protrusion compared to the maxilla in the sagittal and transverse planes. Skeletal and dentoalveolar relationships are Class III according to Angle, which is most often the consequence of prognathism of the mandible, combined with changes in the teeth, alveolar processes, jaws and the cranial base [1].

In addition to true prognathism, there is also pseudo-prognathism, where the maxilla is underdeveloped compared to average values, as well as forced prognathism, which is functional in nature and occurs due to premature contact between anterior teeth [1]. Mandibular prognathism may seriously compromise some of the basic functions: breathing, chewing, swallowing and speaking. Considering that it is one of the most severe facial disharmonies, Class III malocclusion is

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often accompanied by psychological and social problems [1].

According to Angle's classification, when the skeletal and occlusal relationships are Class III, the mandible and the mandibular dental arch are located mesially in relation to Class I, and the mesiobuccal cusp of the upper first molar is in occlusion with the mesial part of the lower second molar, and the tip of the cusp of the upper canine with both lower premolars. Inverted incisor overlap is usually present as well (in physiological rest position, the lower incisors are positioned in front of the upper ones) [2].

In orthodontic diagnostics, gnathometric analysis is a valuable tool, based on which one can obtain data on the position of the teeth, the shape and development of the dental arches and jaws, and occlusal relationships [1, 3].

The research was aimed to determine the morphological characteristics of persons with Class III malocclusion and dentoalveolar relations according to Angle, to compare the measured and average values, as well as to determine the correlation between the same parameters in the upper and lower jaw.

Material and Methods

The study was conducted at the Dental Clinic of Vojvodina, Department of Jaw Orthopedics, during November and December 2022. This retrospective study included 50 study models obtained from patients of both sexes, aged 8 - 14, who were treated at the Dental Clinic of Vojvodina, chosen by using the method of random selection. The inclusion criteria were existence of a full dental arch and Class III dentoalveolar relationships according to Angle.

Gnathometric analysis included the following parameters in both jaws:

1. Sum of incisors - total incisor width measured in the mesiodistal direction;
2. Anterior width of the dental arch - interpremolar distance;
3. Dental arch height - distance from the labial surface of the incisors to the anterior width of the arch;
4. Posterior width of the dental arch - intermolar distance;
5. Dental arch length - distance from the right first permanent molar to the left one measured along the occlusal surfaces;
6. Length of the apical base - distance from the right first permanent molar to the left one measured along the fornix.

We measured the maxillomandibular relationship, as well as the relationships of the length of the maxillary and mandibular dental arches, based on the length of the apical base and the length of the dental arch.

Gnathometric analysis was performed on plaster cast models. To measure the anterior and posterior width, and the height of the arch, Korkhaus three-dimensional calliper was used. To determine the sum of incisors, an ortho-compass with straight arms and a millimetre scale was used. A self-adhesive tape and a ruler were used to measure the length of the apical base, while a copper wire was used to measure the length of the dental arch. Average values were taken from the tables for dental arch analysis according to Schwarz and the table of ideal ratios of the coronary and apical bases lengths according to Rees [3].

The evaluation of the results was carried out by comparing the measured values with the corresponding average values from the tables according to Schwartz and Rees.

The statistical analysis of the results included determination of the mean value, standard deviation, minimum, maximum value, Pearson correlation test and t-test with a significance level of $p < 0.05$. The results are presented tabularly.

Results

The research results show that in Class III malocclusions, there is a greater development of the lower and lesser development of the upper dental arch.

Table 1 shows descriptive statistics for all the parameters measured: their mean values, standard deviation, as well as minimum and maximum measured values.

The mean value of the measured sum of maxillary incisors is 31.85 mm, which is a slightly higher than the average of 31.50 mm; however, the difference is not statistically significant. The mean value of the measured sum of mandibular incisors is 22.97 mm, which is statistically significantly higher than the average value from the tables of mean values (21.75), $p < 0.05$.

The mean height of the maxillary arch is slightly higher than the average value in the population (19.15 mm). It is 20.15 mm, but the difference is not statistically significant, $p = 0.202$.

The mean value of the height of the mandibular arch is 17.63 mm, which is in the range of the average values in the population (17.50 mm), $p = 0.728$.

The mean anterior maxillary arch width is 37.29 mm, while the mean anterior mandibular arch width is 37.38 mm. In the upper and lower jaw, the anterior width of the dental arch is smaller than the average values in the population, for the same sum of incisors, $p < 0.05$.

The posterior width of the dental arch is smaller in both the upper and lower jaw compared to the average posterior width of the arch (49 mm) for the same number of incisors. The mean posterior width of the upper dental arch is 46.45 mm, while the mean intermolar distance of the lower dental arch is 48.79 mm. The difference is statistically significant for the upper ($p < 0.05$), but not for the lower dental arch. The comparison between the obtained results and the average values in the population is shown in **Table 2**.

The relationship between the measured dimensions of the maxillary apical base and the maxillary dental arch is statistically lower than the values according to Rees and it is 1.1 mm ($p < 0.05$).

The relationship between the mandibular apical base and the mandibular dental arch is 7.25 mm, which is statistically significantly higher than the ideal values according to Rees ($p < 0.05$).

The measured relationship between the maxillary and mandibular apical base is 3.52 mm, which is not statistically significantly different from the recommended Rees values (p = 0.09).

Table 1. Descriptive statistics of measured parameters in millimeters
Tabela 1. *Deskriptivna statistika izmereneih parametara u milimetrima*

	Mean value *Srednja vrednost*	Standard deviation *Standardna devijacija*	Minimum measured value *Minimalna izmerena vrednost*	Maximum measured value *Maksimalna izmerena vrednost*
Sum of maxillary incisors/*Suma gornjih inciziva*	31.85	2.41	29.00	36.00
Sum of mandibular incisors/*Suma donjih inciziva*	22.97	1.63	19.00	27.00
Maxillary arch height/*Visina gornjeg luka*	20.15	2.80	15.50	27.00
Mandibular arch height/*Visina donjeg luka*	17.63	2.24	14.00	24.00
Maxillary anterior teeth width/*Prednja širina gornje vilice*	37.29	3.65	30.50	45.50
Mandibular anterior teeth width/*Prednja širina donje vilice*	37.38	2.44	32.00	42.00
Maxillary posterior teeth width/*Zadnja širina gornje vilice*	46.45	3.25	36.50	52.00
Mandibular posterior width/*Zadnja širina donje vilice*	48.83	2.80	46.00	56.00
Maxillary apical base length to dental arch ratio *Odnos dužine apikalne baze i zubnog luka u gornjoj vilici*	+1.10	4.60	-7.00	+8.00
Mandibular apical base length to dental arch ratio *Odnos dužine apikalne baze i zubnog luka u donjoj vilici*	+7.25	2.53	-1.00	+11.00
Correlation between maxillary and mandibular apical base lengths/*Odnos dužine apikalnih baza gornje i donje vilice*	+3.52	5.28	-9.00	+16.00
Correlation between maxillary and mandibular dental arch lengths/*Odnos dužine zubnih lukova gornje i donje vilice*	+9.51	7.52	-5.00	+30.00

Table 2. Correlation between the measured and average maxillary and mandibular parameters in millimeters
Tabela 2. *Odnos izmerenih i prosečnih, tabelarnih vrednosti parametara u gornjoj i donjoj vilici u milimetrima*

	Measured value *Izmerena vrednost*	Average value *Prosečna vrednost*	Statistical significance *Statistička značajnost*
Maxillary sum of incisors/*Suma inciziva gornje vilice*	31.85	31.50	p=0.58
Mandibular sum of incisors/*Suma inciziva donje vilice*	22.97	21.75	p<0.05
Maxillary arch height/*Visina luka gornje vilice*	20.15	19.50	p=0.20
Mandibular arch height/*Visina luka donje vilice*	17.63	17.50	p=0.72
Maxillary anterior width/*Prednja širina gornje vilice*	37.29	39.00	p<0.05
Mandibular anterior width/*Prednja širina donje vilice*	37.38	39.00	p<0.05
Maxillary posterior width/*Zadnja širina gornje vilice*	46.45	49.00	p<0.05
Mandibular posterior width/*Zadnja širina donje vilice*	48.79	49.00	p=0.72

Table 3. Measured values of the apical base and dental arch parameters in regard to the recommended values according to Rees in millimeters
Tabela 3. *Prikaz izmerenih vrednosti apikalnih baza i dentalnih lukova u odnosu na preporučene vrednosti po Risu u milimetrima*

Measurement *Merenje*	Measured values *Izmerena vrednost*	Ideal values acc. to Rees *Idealne vrednosti po Risu*	Statistical significance *Statistička značajnost*
Correlation between the maxillary apical base length and dental arch length *Odnos dužine maksilarne apikalne baze i zubnog luka*	+1.10	+1.5 to +5.0	p < 0.05
Correlation between the mandibular apical base length and dental arch length/*Odnos dužine mandibularne apikalne baze i zubnog luka*	+7.25	+1.5 to +7.0	p < 0.05
Correlation between the maxillary and mandibular apical base length *Odnos dužine maksilarne i mandibularne apikalne baze*	+3.52	+3.0 to 9,5	p = 0.09
Correlation between the maxillary and mandibular dental arch length *Odnos dužine maksilarnog i mandibularnog zubnog luka*	+9.51	+5.0 to +10.0	p = 0.175

The relationship between the maxillary and mandibular teeth is within the recommended values, given the fact that it is 9.51 mm **(Table 3)**.

The examination of the relations and interdependence of the corresponding parameters in the upper and lower jaw, no statistically significant correlation was found.

The correlation between the sum of maxillary and mandibular incisors is positive, but not statistically significantly high, r = + 0.49.

The correlation between the height of the maxillary arch and the height of the mandibular arch is positive, but not statistically significantly high, r = + 0.36.

The correlation between the height of the maxillary and mandibular arches is positive, but very low r = + 0.20.

The correlation between the posterior width of the maxillary and mandibular arches is positive, but has no statistical significance, r = + 0.32.

The correlation between the length of the apical bases of the maxilla and mandible is positive, but not statistically significantly high, r = + 0.38.

The correlation between the length of the dental arches of the maxillary and mandibular is positive, but very low, r = + 0.048.

Discussion

Gnathometric analysis of the study models, whether they are cast or digital, is an indispensable diagnostic method by which, without exposing the patient to X-ray radiation, data are obtained to establish the diagnosis and determine the treatment plan. As a research method, it is present in contemporary research on the morphological characteristics of malocclusions in different populations [2, 4–8].

The etiology of Class III malocclusions is a current and insufficiently researched issue [9]. The major cause of malocclusion is the disproportion between the size of the jaws and the teeth on the one hand, and the disproportion between the size of the upper and lower jaw on the other [1]. As a consequence of the disproportion between the jaws, in the case of prognathism of the lower jaw, a bilateral crossbite or an open bite may occur. In the lower dental arch, a coronal crowding in the front may appear due to retroclined incisors, with or without compensatory proclination of the upper incisors [10–12]. These factors are determined by the ratio of the apical base length to the coronally measured length of the dental arch, as well as the mesio-distal dimension of the tooth, i.e., the overall width of the incisors.

The results of this research confirm the previously described characteristics typical of Class III. The sum of mandibular incisors in the examined sample is significantly higher, while the sum of maxillary incisors is within the average values. A study conducted in Iraq also indicates that there is a relationship between the development of the dental arch and the size of the teeth and that the sum of mandibular incisors in Class III subjects is greater than the same parameter in Class I occlusion subjects [11].

The mean maxillary sum of incisors is 31.85 mm, while the mean mandibular sum is 22.97 mm. Mean values were also measured in studies in Niš. The result of the mean mandibular sum of incisors in the Niš research was 23.1 mm, while the Novi Sad research obtained slightly higher values of 24.7 mm and 24.9 mm [13–16]. The presented findings also correspond to the anthropological measurements conducted in Republika Srpska, where the measured mandibular sum of incisors was 22.88 mm [17]. The mean values of the maxillary sum of incisors in the same studies ranged from 30.17 mm to 32.12 mm [14, 15].

Numerous studies have come to the conclusion that prognathism inhibits the development of the upper jaw and the upper dental arch to a greater or lesser extent [11]. The values of our research, such as the lower value of the upper dental arch posterior width, as well as the lower value of the maxillary apical base to the dental arch ratio, point to a lower development of the upper jaw.

Studies in Niš, Korea and Turkey indicate that people with Class III malocclusion have a significantly smaller maxillary dental arch size [18–21]. Measurements of the anterior and posterior width of the dental arches in numerous studies in America, Turkey and Croatia also show significantly greater development of the lower dental arches [21–24].

A statistically significantly higher ratio of the mandibular apical base and arch length is also one of the characteristics of Class III malocclusion, which was confirmed by our research. It is believed that due to the lingual inclination of the lower teeth, the outer surface of the mandibular base forms a larger arch and this determines the longer length of the apical base compared to the length of the dental arch [25].

Moreover, the ratio of the maxillary and mandibular apical base is very low, as it is at the lower threshold of the Rees interval and very close to statistical significance (p = 0.09), which also indicates a greater development of the lower jaw and dental arch.

Similar studies by other authors mostly confirm our results. Greater dimensions of the dental arch in individuals with Class III malocclusion were obtained in Korea and China [19, 20, 26].

It is considered that the dimensions of the dental arches are largely determined by the size of the teeth, so it can be concluded that the size of the teeth as well as the dimensions and shape of the dental arches indicate available space in the jaw, the prognosis of esthetics and results of the therapy, and that they largely guide the diagnosis and therapy plan in orthodontics.

The limiting factor of this study is the fact that there were only a few relevant data from the research conducted in the last 5 years that we could compare our results to.

Conclusion

The research showed that Class III malocclusion is statistically significantly different compared to average values in accordance with the following characteristics:

– Greater sum of mandibular incisors

– Smaller anterior width of both dental arches
– Smaller posterior width of the maxilla
– Smaller maxillary length of the apical base to the dental arch ratio

– Greater mandibular length of the apical base to the dental arch ratio.

No correlation was established between the corresponding parameters of the upper and lower jaw.

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DEFINING THE BREAKDOWN VALUE OF VITAMIN B12 AS AN IMPORTANT FACTOR IN THE DEVELOPMENT OF MILD COGNITIVE IMPAIRMENT

DEFINISANJE PRELOMNE VREDNOSTI VITAMINA B12 KAO ZNAČAJNOG FAKTORA U NASTANKU BLAGOG KOGNITIVNOG OŠTEĆENJA

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Summary

Introduction. The aim of our research is to determine the breakdown value of vitamin B12 in the blood that causes mild cognitive impairment. **Material and Methods.** Two hundred respondents participated in this research. Using screening tests, mild cognitive impairment was found in 50 patients, while in 150 patients the cognitive function was preserved. Borderline values and units of vitamin B12 concentration were determined according to the standards of the local laboratory and their reference values ranged from 138.00 to 652.00 pmol/l. **Results.** Using the t-test for independent samples, it was determined that there was a statistically significant difference in the values of vitamin B12 in relation to whether or not the respondents had mild cognitive impairment ($p = 0.000$), i.e. that respondents with mild cognitive impairment – 225.66 had significantly lower values of vitamin B12 than those without mild cognitive impairment – 421.06. The statistic analysis revealed that the area under the receiver operating characteristic curve was significantly above 0,5 (0.968) and this result was statistically significant ($p < 0.0005$). The breakdown value of vitamin B12 was determined as the maximum product between sensitivity and specificity. **Conclusion.** In this research, we determined that there was a statistically significant difference in the values of vitamin B12 in relation to whether or not the respondents had mild cognitive impairment. Being a significant risk factor for mild cognitive impairment, we defined the breakdown value of vitamin B12 which induces mild cognitive impairment of 300.5 pmol/l.

Key words: Vitamin B 12 Deficiency; Homocysteine; Cognitive Dysfunction; Signs and Symptoms; Risk Factors; Reference Values

Sažetak

Uvod. Cilj našeg istraživanja je utvrđivanje prelomne vrednosti nivoa vitamina B12 u krvi koja uzrokuje pojavu blagog kognitivnog oštećenja. **Materijal i metode.** U ovom istraživanju učestvovalo je 200 ispitanika. Pomoću skrining testova kod 50 pacijenata utvrđeno je blago kognitivno oštećenje, a 150 je bilo očuvane kognitivne funkcije. Granične vrednosti i jedinice koncentracije vitamina B12 određene su prema standardima lokalne laboratorije i njihove referentne vednosti kreću se od 138 do 652 pmol/l. **Rezultati**. Primenom t-testa za nezavisne uzorke utvrdili smo da postoji satistički značajna razlika u vrednostima vitamina B12 u odnosu na to da li ispitanici imaju ili ne blago kognitivno oštećenje ($r = 0,000$), odnosno da ispitanici koji imaju blago kognitivno oštećenje ($M = 225,66$) imaju značajno niže vrednosti od onih koji nemaju kognitivna oštećenja ($M = 421,06$). Statističkom analizom utvrđeno je da je površina ispod *receiver operating characteristic* krive znatno iznad 0,5 i iznosi 0,968 i ovaj rezultat je statistički značajan ($r < 0,0005$). Prelomna vrednost vitamina B12 određena je kao maksimalni proizvod između senzitivnosti i specifičnosti. **Zaključak**. U ovom istraživanju utvrdili smo da postoji satistički značajna razlika u vrednostima vitamina B12 u odnosu na to da li ispitanici imaju ili nemaju blago kognitivno oštećenje i kao značajan faktor rizika definisali smo prelomnu vrednost vitamina B12 kod ispitanika koja određuje pojavu blagog kognitivnog oštećenja i koja iznosi 300,5 pmol/l.

Ključne reči: deficit vitamina B12; homocistein; kognitivna disfunkcija; znaci i simptomi; faktori rizika; referentna vrednost

Introduction

It is known that vitamin B12 deficiency is a risk factor for cognitive impairment but it is not clear what the limit is, regarding a great range and influence of other factors. The level of vitamin B12 in blood for adult persons ranges from 200 - 600 pg/ml or 150 - 650 pmol/l, which may vary depending on the method by which it is determined.

Vitamin B12 (cyanocobalamin and hydroxocobalamin) is a compound which contains cobalt and in the body it turns into important coenzymes: methylcobalamin and deoxyadenosylcobalamin. The term cyanocobalamin is usually used for vitamin B12, because most of this substance enters the organism just in this form.

Researches have shown that vitamin B12 deficiency, besides hematological and gastrointestinal disorders, may lead to neuropsychiatric disorders and symptoms such as: neuropathy, cerebellar ataxia, dementia and mood disorders, occurring as a result of its insufficient intake, inadequate absorption or reduced usage. Accurate limit value which causes these disorders in an organism has not still been precisely defined.

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Abbreviations

MCI – mild cognitive impairment
ROC – receiver operating characteristic
HoloTC – holotranscobalamin
MMA – methylmalonic acid
Hcy – homocysteine
ALT – alanine transaminase
AST – aspartate aminotransferase

Cyanocobalamin participates in the metabolism of amino acids, regeneration of myelin and creation of bone marrow cells. Its deficiency causes degeneration of the lateral and dorsal columns of the spinal cord with consequent neuropathy. The cognitive dysfunction of these patients is often followed by irritability, depression, and in some cases psychoticism [1–3].

Neurological symptoms and disorders caused by the deficiency of vitamin B12 are various. In the nervous system, vitamin B12 acts as a coenzyme for L-methylmalonyl-CoA mutase which is necessary for the synthesis of myelin and thus its deficiency leads to myelin synthesis disorders. Vitamin B12 deficiency may cause combined neuropathy and myelopathy. The most frequent neurological manifestation of vitamin B12 deficiency is subacute combined degeneration caused by the degeneration/demyelination of lateral and dorsal columns of the spinal cord and neuropathy. The changes are most frequently seen in the cervical and thoracic areas, but they may occur in any part of the central nervous system except for the brain stem. The symptoms of neuropathy and medullopathy can appear separately or combined and they often precede the symptoms of anemia and cognitive dysfunction.

Cognitive dysfunction is manifested as mild cognitive impairment (MCI) or dementia. Vitamin B12 is important in the synthesis of S-adenosylmethionine, an important methyl donor in many reactions on the level of the central nervous system. Insufficient synthesis of S-adenosylmethionine can reduce the synthesis of monoamine neurotransmitters, and S-adenosylmethionine has an antidepressive function. The deficiency of vitamin B12 may present as episode of psychosis. Although such episodes are mostly seen in elderly and middle aged persons, psychotic episodes have also been described in adolescents [4, 5].

The clinical presentation may vary from behavior disorders, emotional distancing, psychomotor disorders, visual and audio hallucinations, insomnia, distrust and high levels of suspiciousness, believing things that are not based on reality, depression and anxiety, to suicidal thoughts. In persons with MCI, not all cognitive functions are impaired and they may not affect everyday functioning, thus they do not fulfill the main criteria for diagnosing dementia [6–8].

If MCI is established, it is necessary to determine its etiology, because timely diagnosis and determination of the main risk factors may lead to early and complete cure of the patient. One of the possible reasons for these symptoms is vitamin B12 deficiency which can be simply supplemented "per os" and by parenteral therapy [9–13].

The aim of our research was to determine the breakdown value of vitamin B12 in the blood that causes MCI.

Material and Methods

In this research we analyzed prospectively collected data by using methods of descriptive statistics and testing the hypothesis by t-test. Descriptive statistics included measures of central tendency and variability.

Two hundred respondents participated in the research. The following screening tests were used: mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA) and Lawton instrumental activities of daily living (IADL) scale. Of 200 participants, MCI was found in 50 patients and 150 had a preserved cognitive function. In all the examinees, concentration of vitamin B12 in the serum was determined by using a routine method of clinical biochemistry, in an authorized laboratory of the Health Center. The limit values and units of concentration of vitamin B12 were determined by standards of the local laboratory. They were determined by taking blood samples and analyzing serum by chemiluminescent microparticle immunoassay (CMIA) (analyzer Abbot Alinity) and their reference value ranged from 138.00 to 652.00 pmol/l. This value was expressed as numerical continuous value.

To determine the cutoff value of vitamin B12 for determining MCI, we used the receiver operating characteristic (ROC) curve and the intersection of values based on the maximum product of sensitivity and specificity.

Results

The respondents were divided into two groups in regard to MCI. There were 50 respondents (25%) with MCI and 150 respondents (75%) in the control group without MCI.

The respondents were aged between 35 and 65 years, and the average age was 54.18 ± 5.90 years. The respondents in the study group were aged between 45 and 60 years, and the average age was 55.34 ± 3.85 years, while in the control group the respondents were aged between 35 and 65 years, and the average age was 53.79 ± 6.41 years.

The levels of vitamin B12 ranged from 73.8 to 1476.0, and the average level was 372.2 ± 153.1. The levels of vitamin B12 in the study group ranged from 73.8 to 326.6, and the average level was 229.9 ± 55.5, while in the control group the levels of vitamin B12 ranged from 198 to 1476, and the average level was 419.6 ± 145.8.

Among the respondents, there were 98 males (49%) and 102 females (51%). The study group included 24 males (48%) and 26 females (52%), while in the control group there were 74 males (49.3%) and 76 females (50.7%) **(Table 1)**.

By applying the t-test for independent samples, it was determined that there were statistically significant differences in the levels of vitamin B12 in respondents with and without MCI ($p = 0.000$). The respondents with MCI – 225.66 had significantly lower levels of vitamin B12 than those without MCI – 421.06 **(Graph 1)**.

Table 1. Descriptive statistics of the incidence of mild cognitive impairment in relation to gender and marital status
Tabela 1. *Deskriptivna statistika učestalosti blagog kognitivnog oštećenja u odnosu na pol i bračni status*

		All respondents/*Svi ispitanici*		MCI +/*BKO* +		MCI -/*BKO* -	
		No. *Broj*	Percentage *Procenat*	No. *Broj*	Percentage *Procenat*	No. *Broj*	Percentage *Procenat*
Sex *Pol*	Male/*Muško*	98	49	24	48	74	49.3
	Female/*Žensko*	102	51	26	52	76	50.7
Marrital status *Bračni status*	Unmarried *Nije u braku*	19	9.5	3	6	16	10.7
	Married/*U braku*	147	73.5	39	78	108	72
	Widowed/*Udovac*	34	17	8	16	26	17.3

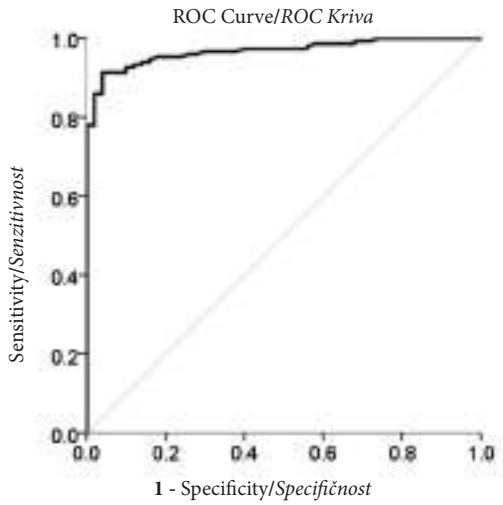
Legenda: BKO – blago kognitivno oštećenje

Graph 1. Level of vitamin B12 in the serum
Grafikon 1. *Nivo vitamina B12 u serumu*
MCI +* - Respondents with MCI)*/Ispitanici koji imaju* ***blago kognitivno oštećenje;* *MCI−*- Respondents without MCI*/Ispitanici koji nemaju blago kognitivno oštećenje*

The respondents with MCI had significantly lower levels of vitamin B12 than those wothout MCI. The breakdown value was determined as a maximum product between sensitivity and specificity **(Graph 2)**. The area below the curve was considerably above 0.5 and amounted to 0.968 and this result was statistically significant ($p < 0.0005$) **(Table 2)**. The breakdown value of vitamin B12, in order to establish MCI of the respondents, was 300.5 (approximate whole number was 300).

Discussion

Vitamin B12 deficiency due to insufficient intake, inadequate absorption and usability is an important risk factor for hematological, gastroenterological and neurological diseases. It is known that B12 deficiency leads to cognitive impairment. The aim of this study was to determine the limit value of B12 which predisposes cognitive impairment.



Graph 2. Maximum product of sensitivity and specificity
Grafikon 2. *Maksimalni proizvod osetljivosti i specifičnosti*

According to the European Food Safety Authority, the recommended adequate amount of vitamin B12 for adults is 4.0 μg/daily. Many scientists have been studying optimum levels of vitamin B12 in blood, as well as its bio-markers.

In the paper on the metabolism and concentration of vitamin B12, Obeid, R. et al. determined that the efficiency of vitamin B12 absorption from food was 40% and daily loss was between 2 and 6 μg/d, and daily intake of free cyanocobalamin of only 1.5 - 2.5 μg during approximately 4 - 6 months could increase vitamin B12 in plasma by 50 - 100 pmol/L [14, 15].

In a study including 98 Danish women in postmenopause, Bor et al. reported that the intake of 6 μg/d

Table 2. Sensitivity and specificity of vitamin B12 level
Tabela 2. *Osetljivost i specifičnost za nivo vitamina B12*

Area *Površina*	St. error *Std. greška*	p *p*	95% confidence interval/*95% interval poverenja*	
			Lower bound/*Donja granica*	Upper bound/*Gornja granica*
.968	.011	.000	.947	.989
Area under the curve/*Površina ispod krive*				
Test result variable(s): Level of vitamin B12 in the blood/*Varijabla(e) rezultata testa: nivo vitamina B12 u krvi*				

of vitamin B12 was sufficient for maintenance of the highest concentration of vitamin B12 and holotranscobalamin (holoTC), and the lowest concentration of methylmalonic acid (MMA) and homocysteine (Hcy) with median (25 - 75 percentile) of 380 (270 - 480) pmol/L for vitamin B12, 119 (92 - 162) pmol/L for holoTC, 0.12 (0.14 - 0.17) μmol/L for MMA and 9.8 (8.3 - 11.4) μmol/L for Hcy compared to the intakes lower than 6 μg/d [16]. A similar study including 299 healthy persons in the USA, found that the medium levels of vitamin B12 and holoTC were the highest in the ranges of intake between 4.2 and 7.0 μg/d, while the MMA and Hcy in plasma reached the lowest levels in subjects who achieved the intake of ≥ 7.0 μg/d.d [17].

In a meta-analysis on the association between the intake of vitamin B12 and biomarkers, Dullemeijer C. et al. estimated that doubling the intake of vitamin B12 was associated with higher concentration of vitamin B12 in serum. The difference in the change of vitamin B12 in plasma, regarding the intake of vitamin B12, was equal if the intake of vitamin B12 was > 100 μg/d, which could indicate limited proportional absorption of vitamin B12 from additional high doses [18].

In regard to the wide reference range, some researches point to the harmful effects of B12 high values. It has not been proved that high intake of B12 in food is harmful. Based on the evidence, additional forms of vitamin B12 are considered to be safe and there is no upper intake level of vitamin B12. However, increased concentrations of vitamin B12 in the plasma of persons who do not take additional vitamin B12 are described in studies including patients with various types of cancer, liver diseases or diabetes type 2, which were later attributed to kidney dysfunction [19, 20]. It was proved that clearance of one dose radioactively marked vitamin B12 was stored in patients with kidney dysfunction [21]. The studies conducted in hospital conditions showed that the increased level of vitamin B12 in plasma is associated with increased levels of liver enzymes and creatinine or albuminuria [22] as well as several clinical conditions such as kidney diseases, diabetes, liver disorders (of any etiology), alcoholism or malignancy [23, 24].

The causes of vitamin B12 deficiency and its consequential clinical manifestations, which affect cognition, include a wide spectrum of pathological conditions: reduced intake of vitamin B12 due to stomach pathology, bowel diseases, inborn selective malabsorption of vitamin B12 with proteinuria, chronic pancreatitis, malabsorption caused by medications, in increased needs of a body during pregnancy, hyperthyroidism and presence of tumors [25–28].

The disorders associated with using vitamin B12 play equally important role in vitamin B12 deficiency, like reduced absorption, although these are rare causes. These disorders include inborn deficiency of transcobalamin, with homocystinuria and inborn intrinsic factor deficiency.

Mild cognitive impairment is the intermediate stage between the cognitive changes of normal aging and very early dementia. It is a disorder which precedes dementia and in many persons it causes memory disorders which are mild and do not disable everyday independent functioning, but they are still inappropriate for the patient's age and education. It has been proved in many researches that MCI can be caused by deficiency of vitamin B12.

A high level of homocysteine in blood (hyperhomocysteinemia) is a risk factor for diseases in which metabolism depends on B vitamins. The use of vitamin B12 can reduce the risk of dementia. The vitamin B12 deficiency becomes relevant when cobalamin participates in formation of purine and pyrimidine, affecting cell duplication, in the way that these processes can cause neurological and psychiatric diseases including cognitive impairments and dementia. This can lead to deterioration of subcortical damages which are sometimes reversible and if they are recognized in early phases, the deficiency can be restituted. Cyanocobalamin use has shown favorable outcomes in various clinical and epidemiological studies. The question is, what are the limit values for vitamin B12 deficiency that can be tolerated by an organism, i.e. that do not lead to cognitive impairment and other clinical manifestations.

Vitamin B12, together with vitamin B6 and folic acid, can reduce high doses of homocysteine in blood. The deficiency of vitamin B leads to low enzyme activities for remethylation of homocysteine into methionine. The results of inefficient reaction of methylation contributes to the development of heart diseases, osteoporosis, Parkinson's disease and Alzheimer's disease. Vitamins B are necessary in the synthesis of S-adenosyl methionine and for methylation of deoxyribonucleic acid. Methylation is a key mechanism by which a body deals with toxins, stress and infections.

Between April and October of 2016, a case-control study was conducted in which the Spearman's correlation analysis showed that homocysteine has an important positive correlation with alanine transaminase (ALT) and aspartate aminotransferase (AST), while a negative correlation was determined between homocysteine, Mini-mental status examination score, Wechsler Adult Intelligence Scale - revised by China intelligence quotient, folate and vitamin B12. Lower levels of folates and hiher levels of Hcy and ALT and AST were associated with the risk of MCI. Higher levels of ALT, AST, Hcy and lower levels of folates were independently related to the risk of MCI [29].

Hyperhomocysteinemia is an independent risk predictor of cognitive decline and can be the result of low level of vitamins B12, B6 and folates, while adequate intake of these vitamins can reduce the levels of homocysteine.

A review study of Olaso G. G. et al. aimed to estimate the effects of vitamins B6, B12 and/or folic acid on the levels of homocysteine in patients with MCI. This review showed that the level of homocysteine in plasma of patients with MCI who were taking vitamins B6, B12 and/or supplements of folic acid was reduced and a statistically significant fall was noticed after 1 month of taking supplements. The results confirm that taking supplements of these vitamins may be the option for reducing the level of homocysteine in persons with MCI and higher homocysteine in the plasma [30].

Homocysteine is a risk factor for brain atrophy, cognitive impairments and dementia. Vitamin B12 and folate are necessary for the methylation of Hcy that is a risk factor for brain atrophy, cognitive impairments and dementia.

The study of Fei Ma et al. estimated how the levels of Hcy in the plasma and its biological determinants, folates and vitamin B12 are associated with MCI and Alzheimer's disease in the elderly Chinese population. Low level of folates and vitamin B12 in blood and higher levels of Hcy were connected to MCI and Alzheimer's disease in the elderly Chinese population and the connection was stronger for Alzheimer's disease [31].

The research conducted by Stanetić K. et al. showed that patients with cognitive impairment and dementia are not fully capable of independent functioning due to the frequency of falls. They pointed out the importance of preventing cognitive impairment [32].

Conclusion

In this case-control study, we determined the levels of vitamin B12 in two groups of respondents: a group with and a group without mild cognitive impairment. By applying the t-test for independent samples, we determined that there was a statistically significant difference in levels of vitamin B12 in respondents with and respondents without mild cognitive impairment. As an important risk factor, we defined the breakdown value of vitamin B12 which is associated with the occurrence of mild cognitive impairment of 300.5 pmol/l.

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EFFECTS OF DEPRESSION ON THE FUNCTIONAL WELL-BEING OF PATIENTS WITH BREAST CANCER

UTICAJ DEPRESIVNOSTI NA FUNKCIONALNO BLAGOSTANJE PACIJENTKINJA OBOLELIH OD KARCINOMA DOJKE

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Summary

Introduction. The psychological status of patients with breast cancer is often compromised as a result of chronic exposure to negative emotions and psychological distress after the diagnosis of a malignant disease and conditions such as depression and anxiety may have a direct impact on the functional well-being of breast cancer patients. The aim of this study was to examine whether depression affects the functional well-being of breast cancer patients. **Material and Methods.** This cross-sectional study was conducted in 2021 and it included 71 breast cancer patients treated at the Department of Physical Medicine and Rehabilitation of the Oncology Institute of Vojvodina at the time of examination. The depression subscale of the Serbian version of the Depression, Anxiety and Stress Scale 21, assessing the degree of depression was used to assess depressive symptoms in the participants. The functional well-being was assessed using the Functional Well-Being subscale of the questionnaire for the Functional Assessment of Cancer Therapy - Breast. **Results.** A statistically significant correlation was found between depression and functional well-being ($r = - 0.438$, $p < 0.001$) of the examined patients. The results of the regression analysis showed that the F model was significant ($F (1.69) = 16.366$; $p < 0.001$) and showed 19.2% of the variance. Depression has a significant impact on the functional well-being of breast cancer patients ($\beta = - 438$, $t = - 4.045$, $p < 0.001$). **Conclusion.** Through a multidisciplinary approach, it is important to simultaneously functionally train breast cancer patients, but also to implement timely psychological support and rehabilitation.

Key words: Depression; Depressive Disorder; Breast Neoplasms; Psychological Well-Being; Psychosocial Support Systems; Rehabilitation

Sažetak

Uvod. Psihološki status pacijentkinja obolelih od karcinoma dojke je često kompromitovan kao posledica hronične izloženosti negativnim emocijama i psihološkom distresu nakon postavljene dijagnoze maligne bolesti, a stanja poput depresivnosti i anksioznosti mogu imati direktan uticaj na funkcionalno blagostanje u ovoj grupi pacijentkinja. Cilj ove studije bio je da se ispita da li depresivnost utiče na funkcionalno blagostanje pacijentkinja obolelih od karcinoma dojke. **Materijal i metode.** Istraživanje je sprovedeno tokom 2021. godine i dizajnirano kao studija preseka u kojoj je učestvovala 71 pacijentkinja obolela od karcinoma dojke koja je u momentu ispitivanja bila na kontroli u Službi za fizikalnu medicinu i rehabilitaciju na Institutu za onkologiju Vojvodine. Supskala depresivnosti srpske verzije Skale depresivnosti, anksioznosti i stresa 21 *(engl. The Depression, Anxiety and Stress Scale 21*) koja procenjuje stepen depresivnosti je korišćena za procenu depresivne simptomatologije kod ispitanica. Funkcionalno blagostanje je procenjeno pomoću Supskale funkcionalnog blagostanja (*engl. Functional Well-Being subscale*) Upitnika funkcionalne procene terapije karcinoma (*engl. Functional Assesment of Cancer Therapy - Breast*). **Rezultati.** Utvrđena je statistički značajna korelacija između depresivnosti i funkcionalnog blagostanja ($r = - 0.438$ na nivou značajnosti $p < 0,001$). Rezultati regresione analize pokazuju da je model signifikantan $F (1.69) = 1\ 6.366$; $p < 0,001$ i pokazuje 19,2% varijanse. Depresivnost značajno doprinosi funkcionalnom blagostanju pacijentkinja obolelih od karcinoma dojke ($\beta = - 438$, $t = - 4.045$, $p < 0,001$). **Zaključak.** Kroz multidisciplinarni pristup značajno je istovremeno funkcionalno osposobljavati pacijentkinje obolele od karcinoma dojke, ali takođe i sprovoditi pravovremenu psihološku podršku i rehabilitaciju.

Ključne reči: depresija; depresivni poremećaj; karcinom dojke; funkcionalno blagostanje; sistem psihosocijalne podrške; rehabilitation

Introduction

Breast cancer is the most commonly diagnosed malignant neoplasm among the female population worldwide, with more than 2.26 million new cases in 2020 [1]. According to the data of the World Health Organization, breast cancer is in the first place, accounting for 28.6% of new cases of malignant diseases among the global female population [2]. While the survival rate has increased significantly in recent years, the therapeutic modalities used in the treatment of these patients are often aggressive, and may have numerous side effects on both the somatic and psychological well-being of breast cancer patients [3].

The psychological status of patients is often compromised as a result of chronic exposure to negative

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Abbreviations
QOL – quality of life
DASS 21 – Depression, Anxiety and Stress Scale 21
FACT-B – Functional Assessment of Cancer Therapy - Breast

emotions and psychological distress after the diagnosis of a malignant disease, which is associated with a significantly higher prevalence of psychological disorders among patients with breast cancer in comparison to the general population [4]. Coping with the diagnosis of breast cancer is an important health issue for the patients with numerous challenges. Acknowledging the diagnosis and the forthcoming treatment, learning about the prognosis and the risk of relapse, dealing with the side effects of therapy as well as of uncertain future, are just some of the factors that contribute to distress which can lead to psychological disorders, the most common of which are anxiety and depression [5]. Depression in patients with breast cancer can affect the functional status and compliance of patients, hence significantly affecting their overall quality of life (QOL). It is also a significant factor in the course and outcome of the oncological treatment [4, 6, 7].

Psychological disorders that initially occur in patients with breast cancer are also the consequence of the treatment side effects significantly impairing their overall QOL [8, 9]. Although the clinician's estimates of symptoms and signs are more accurate regarding the treatment side effects, it is the patient's attitude and their perception of their own health that is of great importance [10].

Functional well-being is the ability of an individual to perform everyday activities and to maintain adequate social interactions. In cancer patients, there is an accelerated impairment of functional well-being, and it is usually seen as the impact of the malignant disease and oncological treatment. However, the disease and oncological treatment do not necessarily have a direct impact on the functional well-being, but rather the psychological status of these patients [11].

So far, a large number of studies have examined the effects of psychological factors on the overall QOL in breast cancer patients [12–16].

Given that functional and psychological symptoms may persist for a long time even after the cessation of treatment and disrupt the patient's return to everyday activities, research thus far has shown the importance of treating subjective symptoms in patients with breast cancer [17].

The aim of this study was to examine whether depression has an effect on the functional well-being of patients with breast cancer.

Material and Methods

This cross-sectional study was conducted in 2021 and it included 71 female participants with breast cancer, treated at the Department of Physical Medicine and Rehabilitation of the Oncology Institute of Vojvodina at the time of examination. The research did not include patients who were undergoing chemotherapy, or patients who developed distant metastases, due to the

Table 1. Data from the subscale of the Depression, Anxiety and Stress Scale 21 (DASS 21)
Tabela 1. *Prikaz rezultata Subskale depresivnosti iz Skale depresivnosti, anksioznosti i stresa (DASS-21)*

	Statements/*Stavke*						
Answers *Odgovori*	D1 (3) I couldn't seem to experience any positive feeling at all. *Nisam imala nikakvo lepo osećanje.*	D2 (5) I found it difficult to work up the initiative to do things. *Primetila sam da mi je teško da ostvarim inicijativu i započnem bilo šta.*	D3 (10) I felt that I had nothing to look forward to. *Osećala sam da nemam čemu da se nadam.*	D4 (13) I felt downhearted and blue. *Osećala sam se tužno i jadno.*	D5 (16) I was unable to become enthusiastic about anything. *Ništa nije moglo da me zainteresuje.*	D6 (17) I felt I wasn't worth much as a person. *Osećala sam se da kao osoba ne vredim mnogo.*	D7 (21) I felt that life was meaningless. *Osećala sam da je život besmislen.*
Did not apply to me at all. *Uopšte se ne odnosi na mene.*	25 (35.2%)	32 (45.1%)	40 (56.3%)	25 (35.2%)	28 (39.4%)	40 (56.3%)	47 (66.2%)
Applied to me some of the time. *Odnosi se na mene pomalo.*	31 (43.7%)	22 (31%)	20 (28.2%)	29 (40.8%)	36 (50.7%)	24 (33.8%)	15 (21.1%)
Applied to me a good part of time./*Odnosi se na mene u priličnoj meri.*	13 (18.3%)	16 (22.5%)	10 (14.1%)	12 (16.9%)	5 (7%)	4 (5.6%)	7 (9.9%)
Applied to me most of the time. *Odnosi se na mene skoro uvek.*	2 (2.8%)	1 (1.4%)	3 (1.4%)	5 (7%)	2 (2.8%)	3 (4.2%)	2 (2.8%)
Total/*Ukupno*	71 (100%)	71 (100%)	71 (100%)	71 (100%)	71 (100%)	71 (100%)	71 (100%)

Table 2. Data from the subscale of the Functional Well-Being of the Questionnaire for the Functional Assessment of Cancer Therapy - Breast (FACT-B)
Tabela 2. *Prikaz rezultata Subskale funkcionalnog blagostanja iz Upitnika funkcionalne procene terapije karcinoma (FACT-B)*

Answers *Odgovori*	Statements/*Stavke*						
	GF1 I am able to work (including work at home)./*Sposobna sam da radim (uključujući rad kod kuće).*	GF2 My work (including work at home) is fulfilling./*Moj posao (uključujući i rad kod kuće) daje mi zadovoljstvo.*	GF3 I am able to enjoy life. *Sposobna sam da uživam u životu.*	GF4 I have accepted my illness. *Prihvatila sam svoju bolest.*	GF5 I am sleeping well. *Dobro spavam.*	GF6 I am enjoying the things I usually do for fun./*Uživam u stvarima koje obično radim iz zabave.*	GF7 I am content with the quality of my life right now. *Zadovoljna sam trenutnim kvalitetom svog života.*
Not at all *Uopšte ne*	0	3 (4.2%)	2 (2.8%)	1 (1.4%)	0	4 (5.6%)	3 (4.2%)
A little bit *Malo*	5 (7%)	14 (19.7%)	6 (8.5%)	2 (2.8%)	5 (7%)	4 (5.6%)	7 (9.9%)
Somewhat *Donekle*	18 (25.45)	34 (47.9%)	7 (9.9%)	13 (8.3%)	23 (32.4%)	14 (19.7%)	23 (32.4%)
Quite a bit *Prilično*	30 (42.3%)	19 (26.8%)	31 (43.7%)	30 (42.3%)	29 (40.8%)	28 (39.4%)	25 (35.2%)
Very much *Veoma*	18 (25.4%)	1 (1.4%)	25 (35.2%)	25 (35.2%)	14 (19.7%)	21 (29.6%)	12 (16.9%)
Total *Ukupno*	71 (100%)	71 (100%)	71 (100%)	71 (100%)	71 (100%)	71 (100%)	71 (100%)

potential impact of the aforementioned states on their functional well-being.

Apart from questionnaires on sociodemographic and clinical data, two instruments were used to carry out the research. A Serbian version of the Depression, Anxiety and Stress Scale 21 (DASS 21) was used to assess depressive symptoms **(Table 1)**. This research used a subscale assessing levels of depression in the participants [18]. Functional well-being was assessed using the Functional Well-Being subscale of the Questionnaire for the Functional Assessment of Cancer Therapy - Breast (FACT-B) [19] **(Table 2)**.

The obtained data were processed using the SPSS 21.0 (IBM Corp. in Armonk, NY, USA) statistical software. In addition to descriptive statistics, Pearson's product-moment correlation coefficient was used for the purpose of examining the correlation between variables, while the specific impact of depression on the functional well-being of patients was examined using simple linear regression analysis. The statistically significant value was set at $p < 0.001$.

Results

The eldest participant in this research was 75 years old and the youngest was 29. The average age of participants was 57.86 (SD ± 9.70). Within the research group 8 (10.7%) participants had a primary education, 36 (48%) a secondary, 4 (5.3%) participants hold an associate degree, while 23 (30.7%) participants had a university degree. As for their marital status, 4% of the participants were single, 14.7% were widowed, 8% were divorced, and 68% were married at the time of research. **Table 1** and **Table 2** show the descriptive statistics of the subscales used in this research.

Due to a significant correlation between depression and functional well-being ($r = -.438$, $p < 0.001$) the next step was to assess the specific effects of depression on the functional well-being of patients. The model F was significant ($F(1.69) = 16.366$, $p < 0.001$) and it showed a 19.2% of the variance, meaning that depression had a significant effect on the functional well-being of patients ($\beta = -438$, $t = -4.045$, $p < 0.001$).

Discussion

Despite a significant progress in early detection and treatment of breast cancer, as well as increased survival rates, the QOL of patients may be significantly impaired. Thus far, there have been numerous studies focused on the health-related QOL of breast cancer patients, as a direct consequence of various psychological factors. Therefore, the aim of this research was to focus on examining the impact of depression on one specific aspect of QOL – functional well-being. The analysis of the obtained data showed that there is a connection between depressive symptomatology and functional well-being in the aforementioned group of patients.

The above mentioned results are to a large extent expected, since clinical experience as well as previous research [20–22] indicate that maladaptive psychological states, such as depression, show indisputable effect on the health-related QOL of breast cancer patients. It can be indirect, like not accepting given advice regarding treatment, inadequate compliance with the oncology team and withdrawal from social relations, as well as direct, like cognitive disorders, decreased physical activity, impaired quality of sleep, loss of appetite, nausea, cancer-related fatigue, and also negative perception of the malignant disease itself. Studies of patients with breast cancer have

shown a correlation between mild-to-moderate depression traits and a decreased QOL in all aspects. In their research, Trinca et al. [12] noted that breast cancer patients with depressive symptoms displayed a significantly lower overall QOL. Reyes-Gibby et al. [13] have reached the conclusion that inadequately treated depressive disorders are a decisive factor in the deterioration of physical and social well-being in patients with breast cancer. The research conducted by Didehdar Ardebil et al. [14] shows a significant correlation between depression in patients with breast cancer and most of the factors that impact one's QOL. Those breast cancer patients who had more depressive symptoms were shown to have a reduced overall QOL, i.e. impaired physical, emotional and functional well-being. In their research, Boing et al. [15] showed that depressive symptomatology in breast cancer patients is associated with younger age, type of surgery performed, presence of functional complications, lower level of self-esteem, as well as presence of some other chronic disease. And notably, Galiano-Castillo et al. [16] concluded that there is a significant correlation between depression and pain in the shoulder joint on the affected side, reduced range of motion, swelling of the ipsilateral arm, as well as pain in the area of the postoperative wound.

For this reason, in oncological treatment it is of great importance to focus not only on the functional but also the psychological status of patients. There is an increasing number of rehabilitation programs that show better results in the functional status, overall QOL, and rehabilitation treatment in patients who had a support from the very moment of their breast cancer diagnosis [23–25]. One such example is early rehabilitation program for breast cancer patients at the Oncology Institute of Vojvodina that provides kinesitherapy program during hospitalization, education of patients and a home-based kinesitherapy program [26]. The early rehabilitation program at the Oncology Institute of Vojvodina also offers psycho-oncological support to breast cancer patients and it improves the health-related QOL in all aspects and at all stages of disease and treatment [19, 27].

The results of this research, as well as of other available studies on this topic, have shown that depression affects not only the individual aspects but also the overall QOL in breast cancer patients to a great extent.

Any future research into the QOL of breast cancer patients should include a larger number of participants, and introduce other determining factors, such as the type of therapy carried out, presence of functional complications, or the stage the participants' illness at the time of research, as well as the presence of various other psychosocial factors.

Conclusion

This study has shown how significant the psychological aspect of cancer treatment is, and points to the necessity of introducing routine screening tests for depression and other mental disorders in patients with breast cancer. A timely detection of depressive symptoms in the aforementioned patients, by a relevant oncological team, would significantly improve the overall course and outcome of breast cancer treatment. Health workers themselves have proven to be of great importance in educating, providing psychological support and improving these patients' overall quality of life. Through a multidisciplinary approach, it is important to simultaneously functionally train breast cancer patients, but also to implement timely psychological support and rehabilitation.

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PROFESSIONAL ARTICLES
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EFFECTS OF CIRCADIAN RHYTHM AND DAILY PHYSICAL ACTIVITY ON SHORT-TERM HEART RATE VARIABILITY IN YOUNG HEALTHY ADULTS – A PILOT STUDY

UTICAJ CIRKADIJALNOG RITMA I DNEVNE FIZIČKE AKTIVNOSTI NA KRATKOTRAJNU VARIJABILNOST SRČANE FREKVENCIJE KOD MLADIH ZDRAVIH ODRASLIH OSOBA – PILOT STUDIJA

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Summary

Introduction. Heart rate variability is the leading non-invasive method used for assessing the activity of the autonomic nervous system. Investigation of the changes in the autonomic nervous system activity under the influence of circadian rhythm and daily physical activity can be beneficial to exercise at the best time of the day and at regular time intervals. Furthermore, it can be used to determine the optimal level of total daily physical activity. This study aimed to demonstrate the effects of circadian rhythm and daily physical activity on the autonomic nervous system at rest through short-term measurements of heart rate variability. **Material and Methods**. Fifteen young healthy adults participated in the study. Heart rate variability was measured on three separate occasions. During these visits, heart rate variability measurements were made in the morning, in the afternoon hours following a physically active day, and in the afternoon hours after a physically inactive day. **Results**. Our study showed no significant differences in the parameters of heart rate variability measured at different times of the day. A comparison of heart rate variability values after a physically inactive day and heart rate variability values after a physically active day did not show a significant difference in any of the heart rate variability parameters. **Conclusion**. Short-term measurements of heart rate variability showed no impact of circadian rhythm and daily physical activity on heart rate variability at rest.

Key words: Circadian Rhythm; Activities of Daily Living; Heart Rate; Young Adult; Autonomic Nervous System

Sažetak

Uvod. Varijabilnost srčane frekvencije je vodeći neinvazivni metod procene rada autonomnog nervnog sistema. Ispitivanje promena aktivnosti autonomnog nervnog sistema pod uticajem cirkadijalnog ritma i dnevne fizičke aktivnosti može biti od koristi u plasiranju vežbi u optimalno doba dana i u pravilnim vremenskim intervalima. Takođe se može koristiti za određivanje optimalnog nivoa ukupne dnevne fizičke aktivnosti. Ova studija je imala za cilj da pokaže uticaj cirkadijalnog ritma i dnevne fizičke aktivnosti na autonomni nervni sistem u mirovanju putem kratkotrajnih merenja varijabilnosti srčane frekvencije. **Materijal i metode.** U istraživanju je učestvovalo 15 mladih zdravih odraslih osoba. Varijabilnost srčane frekvencije je izmerena u tri odvojene posete. Tokom ovih poseta, merenja varijabilnosti srčane frekvencije vršena su u prepodnevnim satima, u popodnevnim satima nakon fizički aktivnog dana i u popodnevnim satima nakon fizički neaktivnog dana. **Rezultati.** Naša studija nije pokazala značajne razlike u parametrima varijabilnosti srčane frekvencije merenim u različito doba dana. Poređenje vrednosti varijabilnosti srčane frekvencije nakon fizički neaktivnog dana i vrednosti nakon fizički aktivnog dana nije pokazalo značajnu razliku ni u jednom od pokazitelja varijabilnosti srčane frekvencije. **Zaključak.** Kratkotrajna merenja varijabilnosti srčane frekvencije nisu pokazala uticaj cirkadijalnog ritma i dnevne fizičke aktivnosti na varijabilnost srčane frekvencije u mirovanju.

Ključne reči: cirkadijalni ritam; aktivnosti svakodnevnog života; srčana frekvencija; mlada osoba; autonomni nervni sistem

Introduction

Heart rate variability (HRV) is a physiological phenomenon of heart rate fluctuations over time that is evident in the oscillations in the length of R-R intervals [1]. These variations are a direct consequence of complex interactions between the parasympathetic and sympathetic branches of the autonomic nervous system (ANS) which makes measuring HRV one of the most reliable, simple, and non-invasive methods for measuring ANS activity intervals [1].

Increased HRV usually indicates a dominant parasympathetic activity, good health, and well-being, while reduced HRV is predictive of worse cardiovas-

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Abbreviations

HRV – heart rate variability
ANS – autonomic nervous system
CR – circadian rhythm
DPA – daily physical activity
SDNN – standard deviation of normal-to-normal RR intervals
RMSSD – root mean square of successive differences
HF – high-frequency power
LF – low-frequency power
SD1 – standard deviation of the projection of the Poincaré plot on the line normal to the line of identity
rANOVA – repeated analysis of variance

cular outcomes and greater risk of all-cause morbidity and mortality, as it is linked to predominant sympathetic activity intervals [1]. The HRV values are affected by factors other than ANS activity such as sex, age, circadian rhythm (CR), and daily physical activity (DPA) [2–6]. The CR causes daily fluctuations of HRV, where HRV is expected to be greater during sleep, remain at high values upon waking, and usually decreases during the day [7]. In addition, the circadian fluctuations of HRV are closely related to the DPA level, but this connection is still not fully explored [5]. Namely, DPA affects not only HRV but CR itself, which is explained by the "timer" or "zeitgeber" activity of DPA [8, 9]. Exploring the overall effect of CR and DPA on the human body and measuring it through HRV monitoring may help to determine the best time for physical activity. These findings can also be used to achieve maximum training effectiveness and the fastest post-workout recovery. Long-term HRV recordings have been shown to correctly predict unwanted outcomes such as myocardial infarction, cerebrovascular incidents, and all-cause mortality.

Despite the high prognostic value of long-term HRV measurements, it has not been broadly integrated into mainstream medical care or personal health monitoring, since it is time consuming and expensive [10, 11]. In contrast to long-term HRV analysis, short-term measurements (5 - 30 minutes) provide results almost immediately, making them suitable for patient monitoring and outpatient care [12]. Although short-term HRV has its advantages over long-term measurements, it is underutilized in medical care, because it is a much less-sensitive way for HRV monitoring [10]. While 24-hour HRV Holter measurements showed a diurnal variation of HRV [6, 8], no study has ever evaluated the possibility of detecting diurnal HRV variation using short-term measurements. Therefore, a question arose whether short-term HRV measurements can determine the best time to exercise and evaluate the impact of other stressors, such as DPA, on HRV. This pilot study aimed to demonstrate the effects of CR and DPA on HRV at rest by using short-term HRV measurements.

Material and Methods

The pilot study was conducted between October 2019 and February 2020, at the Functional Testing Laboratory, Department of Physiology, Faculty of Medicine Novi Sad, Republic of Serbia. Approval of the Institutional Ethics Committee was obtained for the pilot study (No. 01-39/139/1). The subjects provided informed written consent to participate in this pilot study.

Fifteen young (21 ± 1-year-old) healthy male adults were included in the study. All participants were non-athletes, that is, they did not compete in any sport that involved strength, speed, and/or endurance, and they practiced only recreational activities that involved light-to-medium physical activity three to five times a week. They were non-smokers and had no significant previous medical history (including family history). To exclude the risk of possible adverse outcomes, each participant underwent a general physical examination before being included in the study. Electrocardiography, resting heart rate, and blood pressure were examined.

Each participant came to the laboratory three times on three different days. On the first occasion, HRV was measured at 10.00 a.m. (morning HRV). On the day before, the subjects did not engage any kind of strenuous physical activity and did not consume alcohol. Also, the subjects had their usual breakfast and did not consume any caffeine on the day of the experiment. Polar Speed Sensor V800 Bluetooth Smart (Polar Electro Oy, Kempele, Finland; production date 2013) was used to obtain a five-minute recording of R-R intervals at rest. On the second visit, the afternoon HRV was measured at 6.00 p.m. after a physically active day (active afternoon HRV). The level of DPA was estimated by using the total amount of steps, measured via the "Pedometer" smart-phone application, the subjects had made prior to HRV measurement. Subjects were considered to have had a physically active day if they made between 7,000 and 10,000 steps. The third and final visit was intended to determine the afternoon HRV after a physically inactive day (inactive afternoon HRV). The measurement was done at 6.00 p.m., while the participants were required to meet a low level of DPA, less than 3,000 steps.

The HRV analysis was performed using the Kubios HRV 2.0 program (Kubios Oy, Kuopio, Finland; production date 2016). The time-domain and frequency-domain parameters, obtained by linear HRV analysis and Poincaré Plot for non-linear analysis, were used [13]. The time-domain parameters included: (1) standard deviation of normal-to-normal RR intervals (SDNN); (2) root mean square of successive differences (RMSSD); and (3) proportion of consecutive RR intervals that differ by more than 50 ms (pNN50). The frequency-domain parameters included: (1) high-frequency (HF); and (2) low-frequency (LF) spectra. The LF/HF ratio was also measured. Regarding parameters obtained by non-linear analysis, only the standard deviation of the projection of the Poincaré plot on the line normal to the line of identity (SD1) was used, since it describes the short-term variability [13].

Collected data were analyzed using the SPSS 28 software (IBM Corp., Armonk, NY, USA). The repeated analysis of variance (rANOVA) was used to test for differences between the relevant parameters. The frequency-domain parameters that were not normally distributed (LF and HF) were logarithmically transformed and then used for rANOVA. The level of significance was set at 5% ($p < 0.05$).

Table 1. Comparison (rANOVA) of the morning HRV, inactive afternoon HRV, and active afternoon HRV
Tabela 1. *Poređenje (rANOVA) jutarnje VSF, popodnevne VSF neaktivnog dana i popodnevne VSF aktivnog dana*

Parameter *Parametar*	Morning HRV *Jutarnja VSF*	Inactive afternoon HRV *Popodnevna VSF neaktivnog dana*	Active afternoon HRV *Popodnevna VSF aktivnog dana*	F	p-value *p-nivo*
SDNN (ms)	68.6 ± 31.3	67.9 ± 24.3	54.3 ± 14.6	2.77	0.080
RMSSD (ms)	43.3 ± 24.7	39.7 ± 19.9	33.3 ± 17.3	1.31	0.271
pNN50 (%)	18.2 ± 21.0	15.6 ± 15.9	14.5 ± 15.7	0.28	0.758
logHF [log (ms^2)]	6.3 ± 1.4	6.2 ± 0.9	5.9 ± 1.1	0.83	0.448
HF (n.u.)	24.1 ± 11.8	24.8 ± 11.0	23.6 ± 13.2	0.07	0.931
logLF [log (ms^2)]	7.5 ± 1.3	7.4 ± 0.5	7.1 ± 0.7	1.11	0.343
LF (n.u.)	75.9 ± 11.8	75.2 ± 11.0	76.4 ± 13.2	0.07	0.931
LF/HF	4.7 ± 2.0	4.1 ± 3.2	4.7 ± 3.2	1.03	0.369
SD1	33.7 ± 25.4	28.1 ± 13.6	23.2 ± 11.2	1.46	0.250

Legend: Morning HRV - morning heart rate variability; Inactive afternoon HRV - afternoon heart rate variability after a physically inactive day; Active afternoon HRV - afternoon HRV after a physically active day; F - ANOVA test; SDNN - standard deviation of normal-to-normal R-R intervals; RMSSD - root mean square of successive differences; pNN50 - percentage of consecutive R-R intervals that differ by more than 50 ms; HF - high-frequency power; LF - Low-frequency power; logHF - logarithmically transformed high-frequency power; logLF - logarithmically transformed low-frequency power; LF/HF: LF/HF ratio; SD1 - standard deviation of the projection of the Poincaré plot on the line normal to the line of identity; ms - milliseconds; n.u. - normalized units

Legenda: Jutarnja VSF – varijabilnost srčane frekvencije izmerena u jutarnjim časovima; Popodnevna VSF neaktivnog dana – varijabilnost srčane frekvencije izmerena u popodnevnim časovima nakon fizički neaktivnog dana; Popodnevna VSF aktivnog dana – varijabilnost srčane frekvencije izmerena u popodnevnim časovima nakon fizički aktivnog dana; F – ANOVA test; SDNN – standardna devijacija normalnih R-R intervala; RMSSD – srednji kvadrat uzastopnih razlika; pNN50 – Procenat konsekutivnih R-R intervala koji se razlikuju za više od 50 milisekundi; HF – visokofrekventna snaga; LF – Niskofrekventna snaga; logHF – Logaritamski transformisana visokofrekventna snaga; logLF – logaritamski transformisana niskofrekventna snaga; LF/HF – LF/HF odnos; SD1 – standardna devijacija projekcije Poinkareovog dijagrama na pravu koja je normalna na liniju identiteta; ms – milisekunde; n.u. – normalizovane jedinice

Results

Table 1 shows the mean values and standard deviations of the morning HRV, inactive afternoon HRV, and active afternoon HRV parameters. No significant difference was observed between any of HRV parameters.

Discussion

In a review article by Sammito et al. [14], the circadian patterns of all HRV parameters were observed. In most cases, values of time-domain HRV parameters were higher during the night and reached their peak value in the second half of sleep due to higher parasympathetic activity [14]. Upon waking, most parameters remained high and then began to decrease as a consequence of increased cortisol levels and higher sympathetic activity throughout the day [14]. Most studies have shown elevated SDNN values during the night, peak values in the early morning hours (between 5.00 a.m. and 7.00 a.m.), a decrease during the late morning hours, and the lowest values during the early afternoon [15–17]. The RMSSD and pNN50, another two indices of total HRV, fluctuated almost simultaneously. Their trend was similar to the SDNN [17]. According to the study of Jarczok et al. [7], the biggest difference in RMSSD values was between 11.00 a.m. and 10.00 p.m. In regard to frequency-domain HRV parameters, the data from other studies were as follows: HF, which reflects parasympathetic activity, reached the highest values during the night, then decreased during the morning hours with the lowest values in the afternoon, between 1.00 p.m. and 7.00 p.m. [18, 19]; LF and LF/HF values, which indicate sympathetic activity, showed an inverse correlation to HF values as their lowest values were during sleep, then rapidly increased on awakening, remained high during the day, and then started to decrease in the evening [18, 19]. Vandewalle et al. [20] and Yamasaki et al. [21] showed elevated LF and slightly elevated HF in the morning, compared to the early evening. The non-linear metric SD1 is identical to the RMSSD parameter [13]. Therefore, the discussion on the SD1 parameter is redundant. In our pilot study, HRV values measured by the short-time method did not show circadian rhythmicity. Two reasons may be responsible for this. Firstly, the sensitivity of short-term HRV measurements is lower than the sensitivity of long-term measurements [10]. Secondly, the time interval between the morning and afternoon HRV measurements was probably not long enough for the short-term measurement method to detect any changes. Other studies that have shown a difference in HRV parameters used longer time intervals between two measurements [14]. Thus, studies should consider measuring HRV values later in the day (after 10.00 p.m.) or earlier in the morning (before 10.00 a.m.) [7, 14]. The level of DPA did not significantly affect any of HRV parameters. Based on other studies, we expected a decrease in HRV as a consequence of the transient elevation of the sympathetic activity induced by exercise in non-athletes [4, 22, 23]. In our study, HRV did not change for two reasons. Firstly, the measuring may have been too short to detect any hormone-induced changes in HRV, so only acute changes in ANS activity could be detected. However, the acute fluctuations of ANS activity at rest were not significant, even after a long day of walking. Secondly, the intensity of DPA may have been too low to

induce a sympathetic response. Therefore, the effect of higher levels of DPA (> 10,000 steps) should be explored. Also, more extended short-term HRV measurements (more than five minutes) could yield different results. Soares-Miranda et al. showed higher values of the mean 24-hour SDNN in people who spend more time walking long distances and doing recreational activities [22]. Accordingly, Zaffalon Júnior et al. showed lower values of RMSSD and increased values of LF/HF ratio in sedentary people [24]. These findings may be attributed to the chronic impact of high levels of physical activity which results in decreased sympathetic activity, an increased vagal tone, and subsequently increased HRV over time. This may be explained by cardiovascular adaptation to an exercise regimen via an increase in maximal cardiac output [25] and via an increase in cardiovascular health in general [26]. In our study, one day of physical activity was not long enough to induce such cardiovascular adaptive mechanisms, and consequently, HRV did not change. Therefore, studies should perform short-term HRV measurements after multiple days of increased DPA levels.

Study limitations

Firstly, this pilot study was limited by the number of participants. Therefore, other studies should include more subjects. Furthermore, a study with subjects of different age, gender, athletic performance, and chronotype should be considered. Finally, because the laboratory was not available at all times of the day, we were not able to measure HRV before 10.00 a.m. and after 6.00 p.m.

Conclusion

Our pilot study failed to detect any heart rate variability changes using short-term (five-minute) measurements. Further research should include different time points of measurements, before 10.00 a.m. and after 10.00 p.m. Also, short-term measurements longer than five minutes should be performed. Different levels of daily physical activity did not affect any heart rate variability parameters. To estimate the effects of daily physical activity on short-term heart rate variability, further research is necessary. Different levels of daily physical activity, longer duration of physical activity before heart rate variability measurements, as well as longer short-term heart rate variability measurements should be evaluated.

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CASE REPORTS
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PURPLE URINE BAG SYNDROME – A SIGN OF URINARY TRACT INFECTION, OR JUST OF URINARY CATHETER BACTERIAL COLONIZATION – A CASE REPORT

SINDROM LJUBIČASTE KESE ZA URIN – ZNAK URINARNE INFEKCIJE ILI SAMO BAKTERIJSKE KOLONIZACIJE URINARNOG KATETERA – PRIKAZ SLUČAJA

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Summary

Introduction. Purple urine bag syndrome is a condition where the urinary catheter bag turns purple as a result of the interaction between bacteria, urine and components of the urine bag. It appears in a certain group of patients with the following risk factors: urinary tract infection, older age, long-term indwelling urinary catheter, constipation, chronic kidney disease. **Case Report.** Two patients with purple urine bag syndrome are presented. The first patient, a 66-year-old man, was hospitalized due to decompensation of alcoholic liver cirrhosis. A urinary catheter was placed on admission, and on the fourteenth day of hospitalization, a purple discoloration of the urine in the urinary bag was noticed. Multidrug-resistant Proteus mirabilis and Enterococcus faecalis were isolated by microbiological analysis of urine. The second patient was a 92-year-old man, hospitalized for acute gastrointestinal bleeding in the form of hematochezia, with an indwelling urinary catheter and a history of a prostate cancer surgery. On the third hospital day, a purple content in the urinary catheter bag was detected and Klebsiella pneumoniae and Morganella morganii were confirmed by bacteriological analysis. Both patients were without clinical and laboratory signs of acute infection. In both cases, the urinary catheter was replaced and ceftriaxone was administered empirically. **Conclusion.** Current guidelines for purple urine bag syndrome recommend catheter replacement and empiric antibiotic therapy. In clinical practice, it is necessary to emphasize that urine sampling for bacteriological analysis is performed only after replacing the catheter, in order to establish the exact etiology of the syndrome and radical use of antibiotics.

Key words: Urinary Tract Infections; Urine; Urinary Catheters; Bacteria; Biofilms; Risk Factors

Sažetak

Uvod. Sindrom ljubičaste kese za urin predstavlja pojavu urina ljubičaste boje u vreći urinarnog katetera kao posledica interakcije bakterija, urina i gradivnih elemenata kese za urin i vezuje se za određenu grupaciju pacijenata sa faktorima rizika za ovo stanje – urinarna infekcija, starije životno doba, dugo plasiran kateter u mokraćnom sistemu, opstipacija, hronična bubrežna insuficijencija. **Prikaz slučaja.** Prikazana su dva bolesnika sa sindromom ljubičaste kese za urin. Prvi bolesnik, muškarac star 66 godina, hospitalizovan je zbog dekompenzacije alkoholne ciroze jetre. Na prijemu je plasiran urinarni kateter, a četrnaestog dana hospitalizacije primećena je ljubičasta prebojenost urina u kesi za urin. Mikrobiološkom analizom urina izolovani su multirezistentan *Proteus mirabilis* i *Enterococcus faecalis*. Drugi bolesnik je muškarac starosti 92 godine, hospitalizovan zbog akutnog gastrointestinalnog krvarenja u vidu hematohezije, sa prisutnim stalnim urinarnim kateterom i istorijom operacije karcinoma prostate. Trećeg hospitalnog dana zbog ljubičastog sadržaja u kesi urinarnog katetera urađena je bakteriološka obrada i verifikovane su *Klebsiella pneumoniae* i *Morganella morganii*. Oba bolesnika su bila bez kliničkih i laboratorijskih znakova akutne infekcije. U oba slučaja zamenjen je urinarni kateter i sprovedena je empirijska terapija ceftriaksonom. **Zaključak.** Aktuelne smernice kao terapiju za ovo stanje navode zamenu katetera i empirijsku antibiotsku terapiju. U kliničkoj praksi neophodno je naglasiti da se tek nakon zamene katetera vrši uzorkovanje urina za bakteriološku analizu, sa ciljem postavljanja tačne etiologije sindroma ljubičaste kese za urin i radikalne upotrebe antibiotika.

Ključne reči: infekcije urinarnog trakta; urin; urinarni kateteri; bakterije; biofilm; faktori rizika

Introduction

Purple urine bag syndrome (PUBS) is a condition where the urinary catheter bag and tubing turn purple as a result of the interaction between bacterial enzymes, elements of the urine, and polyvinyl chloride from the urinary catheter [1]. It is a rare clinical presentation, although among patients in

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Abbreviations
PUBS – purple urine bag syndrome
CRP – C-reactive protein
UTI – urinary tract infection

long-term care institutions with indwelling urinary catheters, it accounts for 9.8% of cases [2, 3].

The pathophysiological basis of PUBS is explained by an entire array of processes in the body, starting with metabolism of amino acid tryptophan. The degradation of tryptophan begins in the intestines, where it is transformed into indole by means of the intestinal flora. Afterwards, indole reaches the liver through the portal circulation, where the final metabolite is obtained through the action of 2 enzymes. First, by the action of the enzyme cytochrome P450 2E 13-hydroxyindole is formed, and then with the help of the sulfotransferase isoform 1A1 of the enzyme indoxyl sulfate (indican) is created. In this form, it is eliminated from the body via the kidneys. In case when indoxyl sulfate in urine makes contact with bacterial enzymes (indoxyl sulfatases or phosphatases), two colored compounds are produced - blue indigo and red indirubin. When they are mixed with polyvinyl chloride, which is a component of the urine bag and urinary catheter tube, a purple shade is obtained [2, 4]. It is thought that alkaline environment and the large number of bacteria in the urine may contribute to the formation of this specific urine color [1]. The geriatric population, people who have mobility difficulties, long-term indwelling urinary catheters, and people with constipation are at increased risk for developing PUBS [5, 6].

Case Report

Our case report presents two patients treated at the Clinic of Gastroenterology and Hepatology, Clinical Center of Vojvodina.

The first patient was a 66-year-old man, admitted due to decompensated alcoholic liver cirrhosis with accumulation of a large amount of ascites. The patient was diagnosed with cirrhosis and complications including portal hypertension, fourth-degree esophageal varices, secondary sideropenic anemia and hypersplenism. He was immobile, and had stage 3 chronic kidney disease as comorbidity. On admission, a urinary catheter was placed due to the patient's condition and the need to measure the 24-hour urine output. On the 14th hospital day, a purple discoloration of the urine in the urine bag was noticed **(Figure 1)**. On the same day, the urine was sent for microbiological examination, the urinary catheter was replaced and intravenous antibiotic therapy with ceftriaxone 2 g/day was initiated. The urine bacteriological analysis revealed two pathogens, both higher in concentrations than 100,000/ml - multidrug-resistant Proteus mirabilis (sensitive only to piperacillin + tazobactam, meropenem, ceftazidime-avibactam, and moderately sensitive (with increased antibiotic exposure) to imipenem, and resistant to tested antibiotics from the group of semi-synthetic penicillins with and without clavulanic acid, first and third generation cephalosporins, fluoroquinolones, aminoglycosides, sulfonamide + trimethoprim) and Enterococcus faecalis (sensitive to teicoplanin, vancomycin, tigecycline and linezolid, and resistant to tested penicillin antibiotics and fluoroquinolones). The patient was afebrile during hospitalization. The laboratory findings showed no increase in inflammation markers: C-reactive protein (CRP) upon admission was 9.6 mg/l (reference values 0 - 5 mg/l), and on the day when purple urine was observed, CRP was 3.2 mg/l. A nephrologist was involved in the treatment due to the retention of nitrogenous substances in the blood. Moreover, during hospitalization the patient had gastrointestinal bleeding in the form of enterorrhagia and endoscopic band ligation was done. Due to anemia, the patient received red blood cell transfusions. In the further course of hospitalization, the patient showed signs of encephalopathy and became hemodynamically unstable with a fatal outcome.

The second patient, a 92-year-old man was hospitalized for acute gastrointestinal bleeding in the form of hematochezia. Esophagogastroduodenoscopy was performed and a Forest Ib duodenal bulb ulcer was found. After hemostasis was achieved with hemoclips and adrenaline solution was infused, the patient was hemodynamically stable, without recurrence of bleeding. Anemia was corrected with red blood cell transfusions. The patient had a chronic kidney failure, a heart pacemaker, and a prostate cancer surgery 30 years ago, with an indwelling urinary catheter. On the third hospital day, it was noticed that the urine in the bag was purple

Figure 1. Purple urine in the first presented patient
Slika 1. *Ljubičast urin prvog prikazanog bolesnika*

Figure 2. Purple urine coloration in the second patient
Slika 2. *Ljubičasta prebojenost urina drugog prikazanog bolesnika*

(Figure 2) and a sample was sent for biochemical and bacteriological analysis. The chemical urine examination revealed alkaline urine (pH 8), specific gravity less than 1.005 (normal values 1.005 - 1.025), cloudy and light purple in color, while the microscopic analysis of urine sediment indicated an increased number of leukocytes (10 - 30 p/HPF, normal up to 5 p/HPF) and erythrocytes (5 - 10 p/HPF, normal up to 5) and a mass of bacteria. Klebsiella pneumoniae (resistant only to penicillin antibiotics) and Morganella morganii (resistant to penicillin antibiotics, trimethoprim + sulfamethoxazole and fluoroquinolones, sensitive to other tested antibiotics) were isolated from the urine sample. Both bacteria were present in numbers over 100,000/ml. The patient was treated with ceftriaxone (2 g/day) administered intravenously; the antibiotic was given empirically, and there was no need for correction according to the antibiogram results. Although the patient did not have a fever, a monitoring of C-reactive protein was performed, and all the time it was within the reference range (on admission < 0.5 mg/l, then 1.3 mg/l). Since the gastrointestinal bleeding was resolved and there was a clinical and laboratory improvement, the patient was discharged from hospital.

Discussion

A change in urine color may indicate various congenital disorders (porphyria, alkaptonuria), but it may also be caused by the use of certain drugs (rifampicin, methylene blue, IV hydroxocobalamin). In elderly people without knowledge about the mentioned congenital diseases, it is more likely that urine discoloration is caused by therapeutic changes or due to PUBS. Taking into account that population at high risk of PUBS development has poor outcomes of catheter-related urinary infections, it is important to emphasize the importance of effective diagnostic assessment and early application of adequate therapy [5]. The data from a review article including 116 cases of PUBS in a 36-year period suggest that there was a decrease in mortality from 6.8% to 4.3% among patients with PUBS in the last few years, which was considered to be a consequence of a prompt and targeted antibiotic therapy [7].

The most common pathogens causing urinary tract infection (UTI) accompanied by PUBS listed in the literature are Escherichia coli, Providentia stuartii, Providentia rettgeri, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus species and Morganella morganii [2, 6], four of which were isolated from the urine of our two patients.

Due to the communication difficulties, we could not obtain any information about the symptoms that would indicate UTI in our patients. Since the patients had neither clinical nor laboratory signs of acute infection, the purple color of urine was the only indication that a microbiological examination of urine was needed. All four bacteria detected in the urine of the presented patients were over 100,000/ml. According to previous research, UTIs associated with PUBS are most often asymptomatic, with a higher number of bacteria per ml of urine, compared to those that are not accompanied by PUBS [8, 9]. Consequently, there is a dilemma on how to interpret PUBS, as a symptom of an UTI or just bacterial colonization of the urinary catheter tube and bag at that moment. A case report from California presented a patient with a drainage catheter in the kidney and urinary bladder (nephrostomy and urostomy) and PUBS. Under the assumption that there was no real infection, only the replacement of the catheters and the bag was performed, without administration of antibiotics, with normalization of urine color afterwards [10]. In order to eliminate the possibility of misinterpretation of laboratory findings, only the first sample after replacing the urinary catheter should be used for biochemical and microbiological analysis.

Our first presented patient had multidrug-resistant strains of bacteria in the urine, which showed sensitivity only to reserve antibiotics according to the antibiogram. Taking into account the moment of urinary catheter placement upon admission and the appearance of purple coloration of the urine in the second week of hospitalization, a hospital-acquired infection is highly suspected. On the other hand, the second patient already had a permanent urinary catheter on admission, purple urine was observed on the third hospital day and a high sensitivity of the isolated bacteria to antibiotics was detected, so it is very likely that the patient already had that infection on admission.

Both presented patients had multiple factors that may have contributed to the development of PUBS, including long-term catheterization, chronic renal insufficiency and mobility difficulties [8]. The appearance of PUBS is more common in people with constipation, which can be explained by the retention of tryptophan in the intestines [3]. In patients with liver cirrhosis, there is a slow movement of contents through the small intestine as well as a change in the gut microbiota in terms of increased bacterial multiplication [11] and there is a possibility that this contributed to the appearance of PUBS in our patient.

In most cases, PUBS is an indolent condition, usually resolved simply by replacing the urinary catheter and antibiotic therapy. However, cases of complicated urinary infections accompanied by this syndrome have been reported in the literature. Moreover, cases of Fournier's gangrene development have been described in repeated PUBS and it is also associated with increased mortality [1, 5, 12].

Recommendations for the treatment of this condition are limited to urinary catheter replacement and empiric antibiotic therapy per os, while intravenous antibiotic administration is reserved for patients with recurrent PUBS and immunocompromised patients [1]. In our two patients, considering the clinical assessment (immunological status of the patient with cirrhosis and increased risk of the patient with sideropenic anemia for developing UTI) [7, 13, 14], it was decided to empirically introduce antibiotic therapy as soon as purple urine was observed. The choice was intravenous application of antibiotics due to the general condition of the patient with cirrhosis and to bypass the gastrointestinal tract in the bleeding patient.

Conclusion

To our knowledge, there are still no definitive guidelines for the treatment of purple urine bag syndrome, but current recommendations emphasize the importance of preventive measures in terms of handling and regular catheter replacement. Previous studies dealing with this condition suggest the replacement of the urinary catheter and the bag as the first step in the therapeutic algorithm. However, according to the literature, it is necessary to place a new catheter first and only then take a urine sample for analysis. In case the bacteriological test of urine sampled in this way is positive, it indicates the presence of bacteria in the urinary system. On the other hand, the possibility of misinterpreting bacterial colonization of the urinary catheter as a urinary tract infection would be avoided. This would contribute to a more accurate diagnosis of urinary tract infection and a more rational use of antibiotics. When deciding whether to introduce antibiotic therapy and to what extent an individual approach is necessary, it is necessary to take into account the entire clinical condition of the patient.

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UNUSUAL PRESENTATION OF DERMAL MICROCALCIFICATIONS ON MAMMOGRAPHY IMAGES – A CASE REPORT

NEUOBIČAJEN PRIKAZ MIKROKALCIFIKACIJA KOŽNOG POREKLA NA MAMOGRAFSKIM SNIMCIMA − PRIKAZ SLUČAJA

Sonja LUKAČ[1, 2], Maja STANKOV[1, 2], Dijana NIĆIFOROVIĆ[1, 2], Jelena PILIPOVIĆ GRUBOR[1], Daniela DONAT[1] and Tijana MRĐANIN[1]

Summary
Introduction. Calcifications and microcalcifications are mineral deposits in the breast tissue. Breast calcifications are a common mammographic finding, present on over 80% of images, and they are usually benign. Characteristics such as size, shape, number, distribution pattern, location, density, and other findings help determine the pathology. Dermal calcifications of the breast are superficial and benign calcifications that are usually found on the sebaceous glands of the skin. In some cases, calcifications can be the first marker of underlying cancer development. They may be associated with the presence of ductal carcinoma in situ or even invasive ductal carcinoma that has spread to the surrounding breast tissue. By correct identification of benign calcifications as such, unnecessary interventions and use of limited resources can be avoided. **Case Report.** A 66-year-old female patient presented for a regular mammography check-up. On the previous mammographic examination, she was categorized as bilateral breast imaging reporting and data system 1. The new mammography images showed numerous newly formed grouped microcalcifications at the junction of the lower quadrants of the right breast, and a stereotactic vacuum-assisted biopsy was indicated. During the biopsy attempt, the image guided biopsy program did not detect any calcifications in the parenchyma or in any projection and therefore it did not allow the biopsy procedure to continue after several attempts. Examination of the right breast skin revealed lesions treated by the patient for a few weeks; a repeat mammogram was performed and it was observed that the calcifications were of dermal origin. **Conclusion.** Dermal calcifications are mostly tiny, about the size of skin pores, single or clustered, and often have a calcified rim surrounding a lucent center. However, dermal calcifications deserve a special attention, because they sometimes lack a lucent center and simulate grouped intraparenchymal calcifications that require careful monitoring or biopsy.
Key words: Calcinosis; Skin; Magnetic Resonance Imaging; Biopsy; Stereotaxic Techniques

Sažetak
Uvod. Kalcifikacije i mikrokalcifikacije predstavljaju nakupine mineralnih naslaga na tkivima dojke. Kalcifikacije dojke su čest mamografski nalaz, prisutan na preko 80% slika i obično su benignih odlika. Karakteristike kao što su veličina, oblik, broj, obrazac distribucije, lokacija, gustina i drugi nalazi pomažu u određivanju patologije. Dermalne kalcifikacije dojke su površinske i benigne kalcifikacije koje se obično nalaze na lojnim žlezdama kože. U nekim slučajevima kalcifikacije mogu biti prvi marker osnovnog razvoja raka. One mogu biti povezane sa prisustvom duktalnog karcinoma in situ ili čak invazivnog duktalnog karcinoma koji se proširio na okolna tkiva dojke. Pravilnom identifikacijom benignih kalcifikacija kao takvih može se izbeći nepotrebna intervencija i korišćenje ograničenih resursa. **Prikaz slučaja.** Pacijentkinja, 66 godina, javlja se na redovnu mamografsku kontrolu. Na prethodnom mamografskom pregledu kategorizovana je *Breast Imaging Reporting and Data System* kao 1 bilateralno. Na novim mamografskim snimcima uočavaju se na spoju donjih kvadranata desne dojke novonastale mnogobrojne grupisane mikrokalcifikacije, te je indikovana stereotoksična vakum asistirana biopsija. Prilikom pokušaja biopsije, program aparata nije detektovao ni u jednoj projekciji prisustvo kalcifikacija u samom parenhimu i samim tim nije dozvoljavao da se procedura biopsije nastavi nakon više pokušaja. Posmatranjem spoljašnjosti kože desne dojke uočena je promena koju pacijentkinja tretira nekoliko nedelja unazad, te je načinjen ponovni mamografski snimak gde je uočeno da su kalcifikacije porekla kože. **Zaključak.** Kalcifikacije kože se najčešće opisuju kao sićušne, veličine kožnih pora, pojedinačne ili grupisane; često imaju kalcifikovani rub koji okružuje lucentni centar. Ipak kalcifikacije kože zaslužuju posebnu pažnju jer ponekad nemaju lucentni centar i simuliraju grupisane intraparenhimske kalcifikacije koje zahtevaju brižljivo praćenje ili biopsiju.
Ključne reči: mikrokalcifikacije; koža; magnetna rezonanca; biopsija; stereotaksične tehnike

Introduction

Breast cancer is the most common malignant disease and cause of death among women in the developed world. Despite increasing incidence, survival has improved over the past two decades with rates of up to 80% reported in Western Europe, North America, Japan and Australia, due to a combination of more effective treatments, better supportive care, and earlier detection [1].

Mammography is the most effective method for breast cancer screening. One of the main early symp-

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Abbreviations
SVAB – stereotactic vacuum-assisted biopsy

toms of cancer on a mammogram is the appearance of microcalcifications [2].

Calcifications and microcalcifications are mineral deposits in the breast tissue. Breast calcifications are a common mammographic finding, present in over 80% of images and they are usually benign [3].

Calcifications account for 31% of all breast lesions found by mammographic screening and can occur as benign or malignant breast lesions. Approximately 55% of clinically non-palpable breast cancers have been shown to be associated with calcifications [4].

Characteristics such as size, shape, number, distribution pattern, location, density, and other findings help determine the pathology. Dermal breast calcifications are superficial and benign calcifications that are usually found on the sebaceous glands of the skin. In some cases, calcifications can be the first marker of the underlying cancer development. They may be associated with the presence of ductal carcinoma in situ or even invasive ductal carcinoma that has spread to the surrounding breast tissue.

Proper identification of benign calcifications as such can help to avoid unnecessary interventions and use of limited resources such as stereotactic vacuum-assisted biopsy (SVAB) [5, 6].

Breast SVAB is a modern method that solves the need for a larger tissue sample for histological analysis. The main indications for SVAB are clustered microcalcifications and this method has been shown to be reliable [7, 8].

Case Report

A 66-year-old female patient came for a regular mammography check-up. The previous mammography examination (one year earlier) showed no suspicious clustered microcalcifications or tumor formations, and she was categorized as bilateral breast imaging reporting and data system (BI RADS) 1. New mammography images showed numerous newly formed clustered microcalcifications at the junction of the lower quadrants of the right breast **(Figures 1**

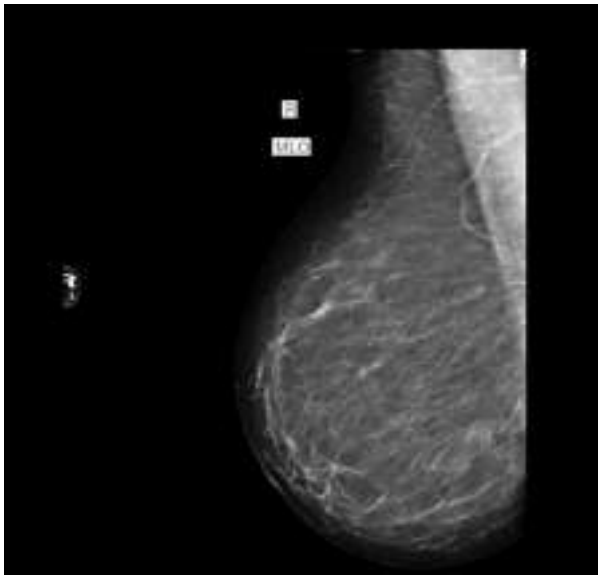

Figure 1. Mediolateral oblique mammography view of the right breast
Slika 1. *Mamografska slika u mediolateralne kose projekciji desne dojke*

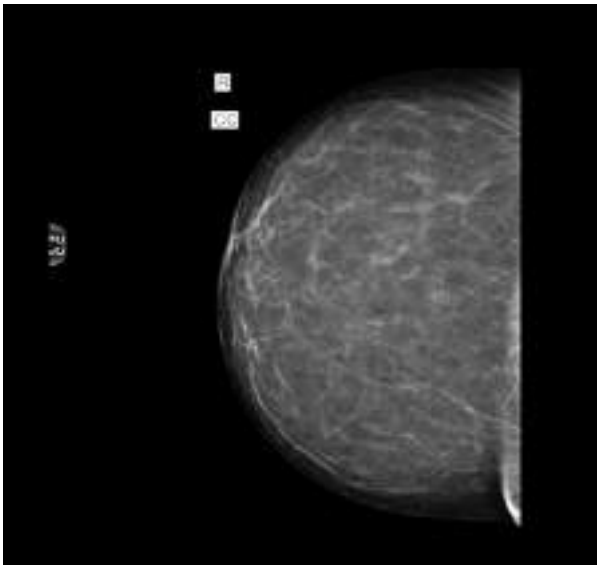

Figure 2. Craniocaudal mammography view of the left breast
Slika 2. *Mamografska slika u kraniokaudalnoj projekciji leve dojke*

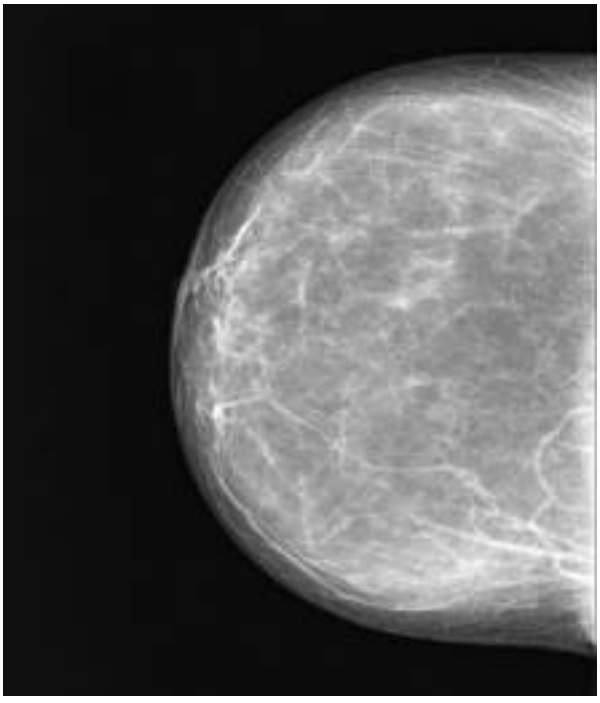

Figure 3. Craniocaudal mammography view of the right breast
Slika 3. *Mamografska slika u kraniokaudalnoj projekciji desne dojke*

and 2). A stereotactic vacuum-assisted biopsy was indicated. During the biopsy attempt, the image guided biopsy device program did not detect any calcifications in the parenchyma or in any projection and therefore it did not allow the biopsy procedure to continue after several attempts. Examination of the right breast skin revealed lesions treated by the patient for several weeks. The patient was offered a dermatology consultation and a recheck after therapy and resolution of the lesion. The patient returned for a follow-up mammogram a month later and the previously described cluster of microcalcifications was not seen, indicating that the calcifications were of dermal origin **(Figure 3).**

Conclusion

Dermal calcifications are mostly tiny, about the size of skin pores, single or clustered, and often have a calcified rim surrounding a lucent center. However, dermal calcifications deserve a special attention, because they sometimes lack a lucent center and simulate grouped intraparenchymal calcifications that require careful monitoring or biopsy.

With the advancement of digital technology, the detectability of microcalcifications has increased as well as the reliability of their classification; however, in some cases it is still difficult for radiologists to correctly differentiate benign from malignant calcifications, especially those classified as breast imaging reporting and data system 3.

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MECHANICAL VALVE THROMBOSIS DURING PREGNANCY – A CASE REPORT

TROMBOZA MEHANIČKE VALVULE TOKOM TRUDNOĆE – PRIKAZ SLUČAJA

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Summary

Introduction. If young women with congenital heart disease need heart valve surgery, it is necessary to thoroughly consider the choice of the valve and the risks of serious complications during pregnancy. **Case Report**. We report a case of a woman who presented with a pregnancy complicated by mechanical aortic valve thrombosis at the end of the first trimester. After a thorough evaluation by a multidisciplinary team, the patient underwent surgical thrombectomy and normal mechanical valve function was restored. At 36 weeks of gestation, planned cesarean section was performed. The mother and the child remained well during the 5-year follow-up. **Conclusion**. Mechanical heart valves in pregnancy carry a very high risk of complications. An individualized approach is needed in the management of women with mechanical valves, as well as uniform antenatal care in centers that provide complete care from pregnancy planning to delivery.

Key words: Pregnancy Complications; Bicuspid Aortic Valve Disease; Heart Valve Prosthesis; Thrombosis; Risk Factors; Anticoagulants; Thrombectomy; Prenatal Care; Treatment Outcome

Sažetak

Uvod. Kada je kod mlade žene sa urođenom srčanom manom indikovana operacija srčanog zaliska, neophodno je detaljno razmotriti izbor valvule i rizike od ozbiljnih komplikacija tokom trudnoće. **Prikaz slučaja.** Predstavljamo slučaj žene čija se trudnoća na kraju prvog trimestra komplikovala trombozom mehaničke aortne valvule. Nakon što je multidisciplinarni tim uradio detaljnu evaluaciju, urađena je hirurška trombektomija i uspostavljena je normalna funkcija veštačkog zaliska. U 36. nedelji gestacije je urađen elektivan carski rez. Tokom petogodišnjeg praćenja i majka i dete su bez tegoba. **Zaključak.** Mehaničke valvule tokom trudnoće nose veoma veliki rizik od komplikacija. Potreban je individualizovan pristup u vođenju trudnoće ženama sa mehaničkim valvulama, ali i jednoobrazna antenatalna zaštita u centrima koji mogu da omoguće kompletno zbrinjavanje od planiranja trudnoće do porođaja.

Ključne reči: komplikacije u trudnoći; bikuspidna bolest aortnog zaliska; mehanički srčani zalistak; tromboza; faktori rizika; antikoagulansi; trombektomija; prenatalna zaštita; ishod lečenja

Introduction

Pregnancy is a hypercoagulable state and presents a high-risk period for women with mechanical heart valves [1]. Several anticoagulation regimens are recommended to achieve adequate anticoagulation, on the one hand, and to prevent bleeding and teratogenicity, on the other [2]. However, just over half of women with mechanical valves end up pregnant giving live birth without complications, and only one-third of them have pregnancy free from any maternal or fetal complications [3, 4]. We present a woman whose pregnancy was complicated by mechanical aortic valve thrombosis and resulted in a good outcome for both the mother and the baby after surgical thrombectomy.

Case Report

A pregnant woman aged 35 years was admitted to the Intensive Cardiac Care Unit of our center due to suspected mechanical aortic valve thrombosis. At the age of 33, she underwent index procedure and a mechanical aortic valve replacement (23 mm St. Jude Medical valve) due to a congenital bicuspid aortic valve. At the time of surgery, she had severe aortic stenosis with concomitant moderate dilatation of the ascending aorta. After isolated valve replacement, she was stable during the follow-up, with a mean gradient of 6.2 mmHg across the prosthesis, and without an increase in aortic diameter measured by echocardiography.

She got pregnant at the age of 35 for the first time and during the 5th week of gestation the acenocoumarol therapy was changed to subcutaneous low molecular weight heparin in a local hospital. She was referred to a tertiary center for expert counseling where a team of cardiologists and obstetricians concluded that the pregnancy was not contraindicated in regard to the cardiac disease, but the maternal risk of cardiac events was significantly increased which was presented to the patient. The coagulation status was followed at a local hospital.

Although she was asymptomatic during the regular checkup at 13 weeks of gestation, physical examination revealed an aortic systolic murmur. Transtho-

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racic echocardiography showed an immobile leaflet of the prosthetic aortic valve **(Figure 1a)**, increased peak (86 mmHg), and mean (49 mmHg) gradients across the prosthesis **(Figure 1b)**, mild aortic regurgitation, dilated ascending aorta with maximal diameter of 46 mm and normal left ventricular ejection fraction. On admission to the Intensive Cardiac Care Unit, transesophageal echocardiography revealed obstruction of one leaflet with a thrombus (5 x 6 mm) and restricted mobility of the other leaflet.

After a thorough evaluation by a multidisciplinary team, the patient underwent surgical thrombectomy at 13 weeks of gestation. No valvular damage was registered after the removal of the thrombus and normal mechanical valve function was restored **(Figure 2)**. The total duration of the non-pulsatile cardiopulmonary bypass was 62 minutes, mild hypothermia of 34◦C was achieved, and the pump flow rate was 3 - 3.5 L/min/m^2. The fetal ultrasound showed a viable fetus with appropriate biometric measurements pre-and postoperatively. Since the patient entered the second trimester, low molecular weight heparin was changed to acenocoumarol. She was discharged 10 days after surgery. At 36 weeks of gestation, she was admitted to the hospital, and a planned cesarean section was performed. Acenocoumarol was changed to subcutaneous low molecular weight heparin in the hospital, four days

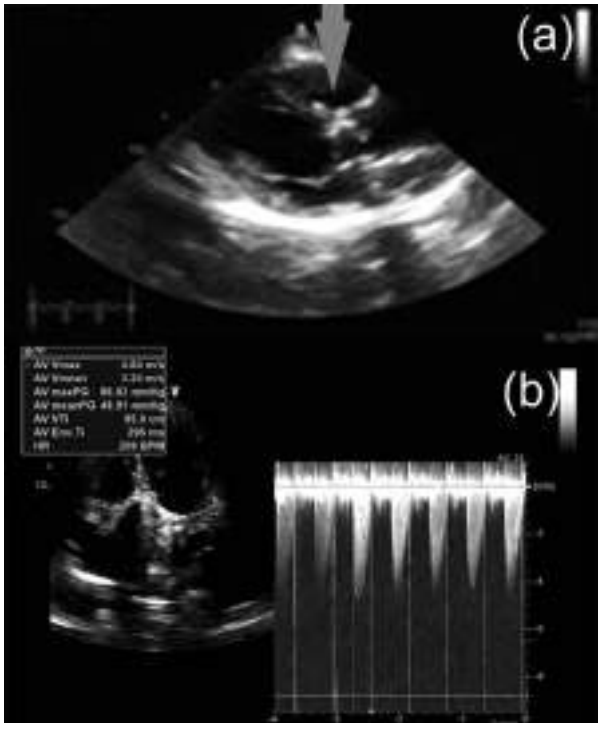

Figure 1. Transthoracic echocardiography: a) Arrow points to the immobile leaflet of the prosthetic aortic valve with a thrombus; b) Elevated maximal (86 mmHg) and mean (49 mmHg) gradients across the prosthesis

Slika 1. *Transtorakalna ehokardiografija. (a) Strelica pokazuje na nepokretan listić veštačke aortne valvule sa trombom. (b) Povišen maksimalni (86 mmHg) i srednji (49 mmHg) gradijent nad valvulom*

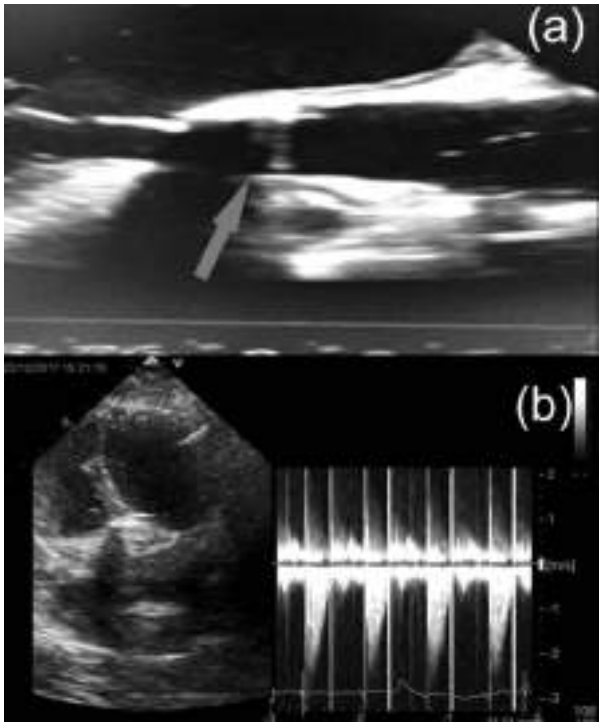

Figure 2. Postoperative echocardiography: a) Transesophageal echocardiography shows normal excursions of mechanical aortic valve leaflets (arrow points to the prosthetic aortic valve); b) Transthoracic echocardiography shows a normal gradient across the prosthesis

Slika 2. *Postoperativni ehokardiografski pregled. (a) Transezofagealna ehokardiografija pokazuje normalne pokrete listića mehaničke aortne valvule (Strelica pokazuje na veštačku aortnu valvulu). (b) Transtorakalna ehokardiografija pokazuje normalan gradijent nad valvulom.*

before surgery. The postpartum period was uneventful. The baby girl had an Apgar score of 9 at 1 minute and 9 at 5 minutes with a birth weight of 2,520 grams. The mother and the baby remained well during the 5-year follow-up.

Discussion

The number of women with congenital heart diseases reaching childbearing age is growing [5]. Considering the fact that there are no randomized clinical trials on pregnant women, we suppose that presentation of each individual case, especially with good clinical outcomes for both the mother and the child, is of great importance in the evaluation of the current guidelines [2]. Although vitamin K antagonists are considered to be most effective in the prevention of mechanical valve thrombosis during pregnancy, they carry the greatest risk of adverse fetal events during the first trimester. In the Registry of Pregnancy and Cardiac Disease, mechanical valve thrombosis was present in 4.7% of 202 pregnant women on heparin and half of the thrombosis cases occurred during the first trimester [1, 3].

The 2018 European Society of Cardiology guidelines for cardiovascular diseases during pregnancy

recommend anticoagulation regimen during the first trimester depending on the dose of vitamin K antagonists. Low doses (warfarin < 5 milligrams per day, acenocoumarol < 2 milligrams per day) should be continued during the first trimester, while higher doses should be replaced with unfractionated heparin or low molecular weight heparin [2]. Guidelines recommend peak anti-Xa levels for low molecular weight heparin dose adjustment, although cases of mechanical valve thrombosis have been reported in appropriately managed patients as well [2, 6]. Moreover, some patients were never monitored for anti-Xa values during the pregnancy [4]. In our case, anti-Xa levels were not monitored, and it was an error in treatment and follow-up of our patient.

Management of thrombotic valve in pregnancy is consistent with the management of non-pregnant patients, with an increased fetal risk [7]. The therapeutic strategy (surgery or fibrinolysis) is an emergency treatment for obstructive left-sided prosthetic valve thrombosis and it carries a substantial risk of complications. Surgery is usually an emergency reintervention and fibrinolysis has a higher risk of bleeding, systemic embolism, and recurrent thrombosis compared to surgery [8]. The optimal time for surgical intervention is between the 13th and 28th week of pregnancy [9]. At the time of surgery, our patient was 13 weeks pregnant without contraindications for surgery. Although fetal loss with cardiopulmonary bypass ranges from 15 to 56%, after a thorough discussion with a multidisciplinary team that involved an obstetrician, a cardiologist, and a readily available experienced surgeon and anesthesiologist, our patient chose surgery [10, 11]. We can say that the timely decision for surgical intervention by experienced staff and a short duration of cardiopulmonary bypass resulted in a favorable outcome for both the mother and the baby.

Vaginal delivery is recommended for most women with cardiac diseases since it is associated with a lower risk of bleeding, infection, and thromboembolic events. Patients with obstetric indications, presenting in labor on vitamin K antagonists, those with aortic diameter more than 45 mm, acute heart failure, or severe pulmonary hypertension have indications for cesarean delivery. Our patient was a high-risk patient (group III, according to the modified World Health Organization classification of maternal cardiovascular risk) regarding aortic pathology and mechanical valve thrombosis [2, 12]. A planned cesarean section was performed to reduce aortic wall stress and to shorten the period without vitamin K antagonists.

Conclusion

In conclusion, mechanical heart valves in pregnancy carry a very high risk of complications, so an individualized approach to the management of women with mechanical valves is required to improve and provide more uniform antenatal care in centers that provide complete care from pregnancy planning to delivery.

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CAVITARY PULMONARY METASTASES – A CASE REPORT

KAVITARNE PLUĆNE METASTAZE – PRIKAZ SLUČAJA

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Summary
Introduction. The lungs are one of the most common sites of metastases from carcinomas and sarcomas. Secondary pulmonary tumors are typically multiple, oval in shape and located in the lung periphery. Cavitation of metastatic pulmonary nodules is extremely rare and most often occurs in primary squamous cell carcinomas of the head and neck and the cervix. **Case Report.** We report the case of a 62-year-old man presenting with dysphagia for solid foods and weight loss in the last two months. The patient had a history of long-term smoking and regular alcohol consumption. A barium meal showed irregular stricture in the proximal esophagus, highly suspicious of malignancy. Computed tomography of the neck and thorax showed tumor infiltration of the cervical and proximal part of the thoracic esophagus and multiple cavitary and solid pulmonary metastases. **Conclusion.** High-resolution computed tomography of the chest and radiological features such as a wall nodules, irregular internal contour of the cavity and spiculated edges allow precise characterization of cavitary metastatic lesions.
Key words: Esophageal Neoplasms; Neoplasm Metastasis; Lung Neoplasms; Carcinoma, Squamous Cell; Tomography, X-Ray Computed

Sažetak
Uvod. Pluća su jedno od najčešćih mesta metastaziranja karcinoma i sarkoma druge lokalizacije. Sekundarni tumori pluća su tipično multipli, ovalnog oblika i periferno lokalizovani. Kavitacija metastatskih plućnih nodusa je izuzetno retka i najčešće se javlja kod primarnih skvamoznih karcinoma porekla glave i vrata kao i grlića materice. **Prikaz slučaja.** Muškarac, star 62 godine, javlja se na pregled zbog disfagije u poslednja dva meseca i gubitka telesne težine. Pacijent navodi da je dugogodišnji pušač i da redovno konzumira alkoholna pića. Načinjena je pasaža jednjaka, gde je uočeno nepravilno, suspektno suženje proksimalnog jednjaka. Na pregledu vrata i grudnog koša kompjuterizovanom tomografijom potvrđena je tumorska infiltracija cervikalnog i proksimalnog dela torakalnog jednjaka. Takođe, uočene su multiple kavitarne i solidne plućne metastaze. **Zaključak.** Kompjuterizovana tomografija pluća visoke rezolucije i radiološke karakteristike promene kao što su iregularnost konture i nodularne promene zida, kao i spikulirane ivice omogućavaju preciznu karakterizaciju kavitarnih metastatskih lezija.
Ključne reči: karcinom jednjaka; metastaze; karcinom pluća; karcinom skvamoznih ćelija; CT

Introduction

The lungs are one of the most common sites of metastases which generally originate from the breasts, colon, kidneys and head and neck region. Secondary pulmonary tumors are typically multiple, oval in shape and located in the lung periphery. Atypical presentations include cavitation, calcification, hemorrhage around metastatic nodules, pneumothorax, air-space pattern, tumor embolism, endobronchial spreading, and solitary masses [1]. Cavitation of metastatic pulmonary nodules is extremely rare and occurs in approximately 4%, most commonly in primary squamous cell carcinomas of the head and neck and the cervix [2].

Case Report

A 62-year-old male was admitted to the emergency department with dysphagia for solid foods and unexplained weight loss in the past two months. The patient had a history of long-term smoking and regular alcohol consumption. Physical examination and laboratory findings were unremarkable. A barium meal showed irregular stricture of the proximal esophagus, highly suspicious of malignancy **(Figure 1)**. Computed tomography (CT) of the neck and thorax showed a tumor infiltration of the cervical and proximal part of thoracic esophagus, necrotic mediastinal and supraclavicular lymph nodes **(Figure 2)**, as well as multiple cavitary and solid pulmonary metastases **(Figures 3 and 4)**. Later, esophagoscopy was performed and squamous cell carcinoma was confirmed by histological examination. Due to coronavirus disease 2019 pandemic, the patient did not come for a follow up and therefore we have no further information about the disease outcome.

Discussion

By definition, a cavity presents a gas-filled space within a pulmonary consolidation, mass, or nodule where the cavity occurs due to drainage of a necrotic component through the bronchial tree [3]. The differential diagnosis of pulmonary cavitary lesions is wide and includes neoplastic, infectious, congenital and

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Abbreviations
CT – computed tomography

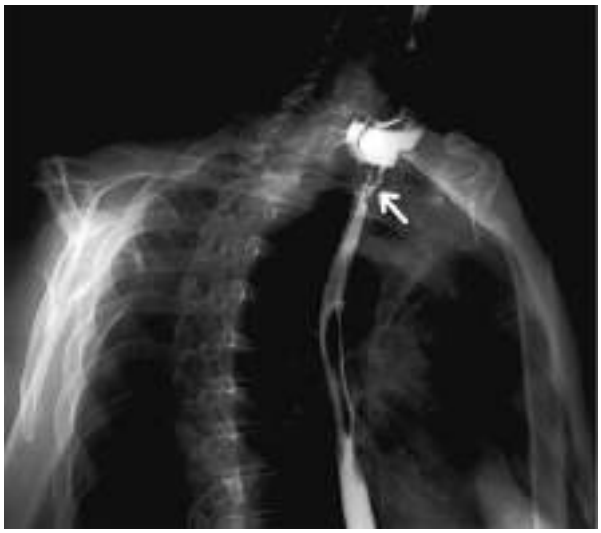

Figure 1. Barium meal showed irregular stricture of the proximal esophagus due to carcinoma (arrow)
Slika 1. *Pasaža jednjaka. Nepravilno suženje proksimalnog jednjaka (strelica)*

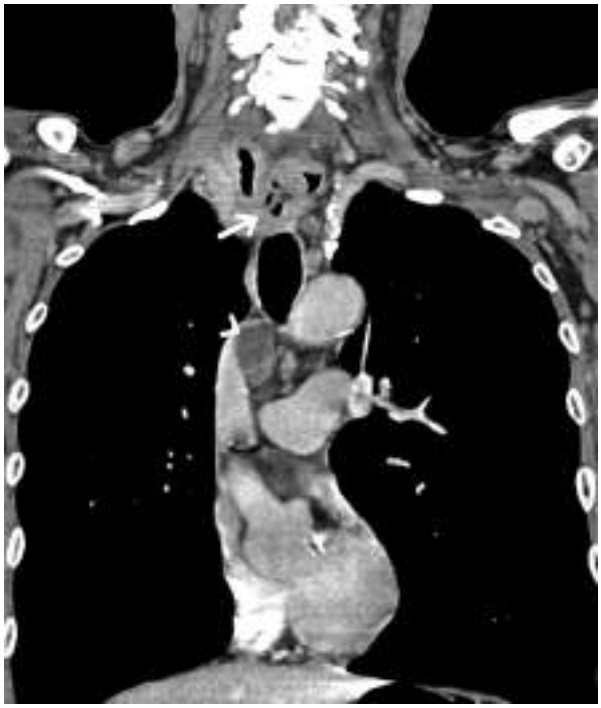

Figure 2. Coronal contrast-enhanced CT image of the neck and thorax; neoplastic infiltration of the cervical and proximal part of the thoracic esophagus (arrow) and necrotic mediastinal lymph nodes (arrowhead)
Slika 2. *Koronalna postkontrastna kompjuterizovana tomografija vrata i toraksa. Tumorska infiltracija cervikalnog i distalnog dela torakalnog segmenta jednjaka (strelica). Nekrotični medijastinalni limfni čvorovi (glava strelice)*

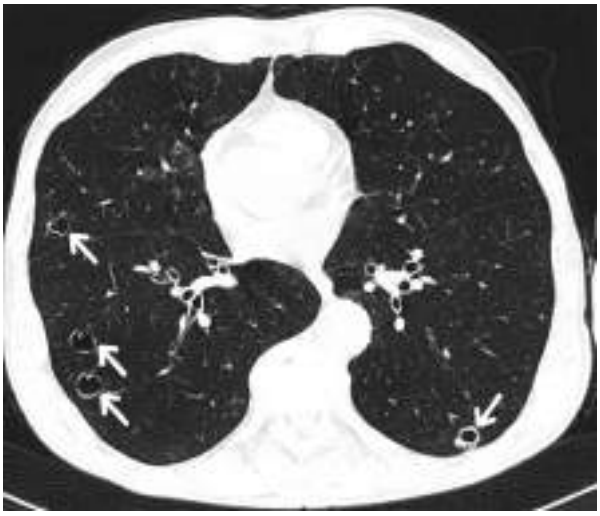

Figure 3. Axial CT image of the thorax (lung window); multiple cavitary pulmonary metastases (arrows)
Slika 3. *Aksijalna kompjuterizovana tomografija toraksa (plućni prozor). Multiple kavitarne metastatske lezije plućnog parenhima (strelice)*

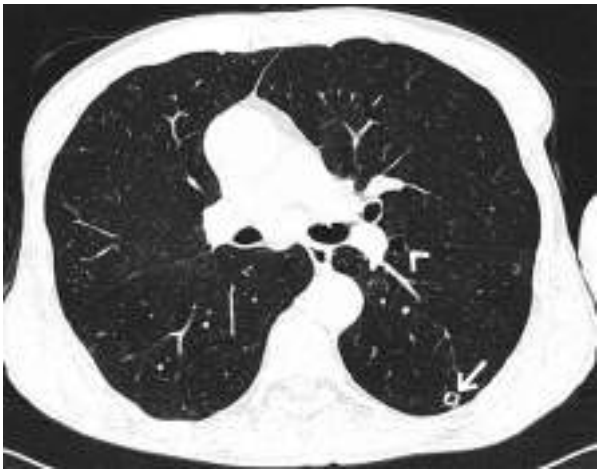

Figure 4. Axial CT image of the thorax (lung window); metastatic cavitary pulmonary lesion with irregular contours and wall nodules (arrow) and cavitary metastasis located centrally (arrowhead)
Slika 4. *Aksijalna kompjuterizovana tomografija pluća (plućni prozor). Metastatske kavitarne lezije plućnog parenhima sa nepravilnom konturom i mekotkivnim nodusima u zidu (strelica). Metastaza lokalizovana centralno u plućima (glava strelice)*

autoimmune diseases as well as pulmonary infarction and septic embolism. A cavitating carcinoma usually has nodular or irregular internal contours due to mural nodules of various size of neoplastic tissue and uneven process of necrosis [4]. Spiculation is often seen in malignant processes due to lymphangitic spread of tumor, fibrosis and local infiltration of the tumor. Moreover, carcinomas tend to invade beyond the interlobular septa, which is rare in benign processes [5].

The period of clinical symptoms can be supportive to make a diagnosis. Acute and subacute processes often include infectious, inflammatory and cardiovascular causes. Cavities with a chronic evolution (> 12 weeks) indicate chronic infections (often mycobacterial or fungal), autoimmune conditions, congenital lesions and malignancy [6]. Malignancy and chronic infections are accompanied by fever, weight loss, long-standing cough and fatigue. Older age, history of smoking and cancer favor the diagnosis of malignancy.

Conclusion

It is crucial to differentiate malignant from non-malignant lesions. High-resolution computed tomography of the chest and radiological features such as wall nodules, irregular internal contour of the cavity and spiculation, help in precise characterization of cavitary lesions. The clinical context such as a patient history and duration of clinical symptoms may also contribute to accurate diagnosis. In uncertain cases, bronchoscopy or computed tomography-guided biopsy and pathological examination are recommended to confirm the diagnosis.

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RESOLVING BLOOD GROUP DISCREPANCY IN A PATIENT WITH ACUTE MYELOID LEUKEMIA – A CASE REPORT

PREVAZILAŽENJE SMETNJI KOD ODREĐIVANJA KRVNE GRUPE U SLUČAJU BOLESNIKA SA AKUTNOM MIJELOIDNOM LEUKEMIJOM – PRIKAZ SLUČAJA

Jasmina GRUJIĆ[1, 2], Nevenka BUJANDRIĆ[1, 2] and Goran MALENKOVIĆ[3]

Summary

Introduction. The ABO blood group antigens are determined by genes located at three separate genetic loci. Loss or weakening of ABO antigens is often associated with hematological malignant diseases, but also solid tumors in the body. A change in the expression of ABO antigens leads to discrepancies when determining the patient's blood group and carries the risk of incompatible transfusions. **Case Report**. During the blood typing of a 27-year-old female patient with a diagnosis of acute myeloid leukemia, there were discrepancies in the interpretation of the ABO blood group. Since the confirmation blood group indicated that it was blood group O, when determining the reverse blood group, the reading showed the absence of the expected agglutination of group A_1 and B red blood cells. By examination of the patient's records, as well as confirmation genotyping, the blood group A was established. After the patient entered the remission phase of the disease, the A Rhesus D positive blood group was determined, without discrepancies during testing. **Conclusion.** Changes in blood groups can occur even before the diagnosis of hematological malignant disease is established. For this reason, it is extremely important to thoroughly examine any discrepancy during blood typing in order to provide patients with safe blood.

Key words: Leukemia, Myeloid, Acute; ABO Blood-Group System; Rh-Hr Blood-Group System; Risk Factors; Blood Grouping and Crossmatching; Blood Group Antigens

Sažetak

Uvod. Antigeni ABO krvnogrupnog sistema determinisani su genima smeštenim na tri nezavisna lokusa. Gubitak ili slabljenje ekspresije ABO antigena često je povezan sa hematološkim malignim bolestima ali i solidnim tumorima u organizmu. Promena ekspresije ABO antigena dovodi do smetnji prilikom određivanja krvne grupe pacijenta i nosi rizik od inkopatibilnih transfuzija. **Prikaz slučaja.** Tokom određivanja krvne grupe pacijentkinji staroj 27 godina, sa dijagnozom akutne mijeloidne leukemije, pojavile su se smetnje u interpretaciji ABO krvne grupe. S obzirom da je konfirmaciona krvna grupa ukazivala da se radi o O krvnoj grupi, prilikom određivanja reverzne krvne grupe očitavanje je pokazalo izostanak očekivane aglutinacije sa test-eritrocitima A_1 i B. Uvidom u dosije pacijentkinje, kao i potvrdnom genotipizacijom, ustanovljena je A krvna grupa. Nakon što je pacijentkinja ušla u remisionu fazu bolesti, određena joj je A krvna grupa, bez neusaglašenosti prilikom testiranja. **Zaključak.** Promene krvne grupe mogu da se dogode i pre nego što je uspostavljena dijagnoza hematološke maligne bolesti. Zato je izuzetno važno da se svaka neusaglašenost prilikom određivanja krvne grupe temeljno ispita kako bi se pacijentima obezbedila bezbedna krv.

Ključne reči: akutna mijeloidna leukemija; ABO krvno grupni sistem; Rh krvno grupni sistem; faktori rizika; krvne grupe i ukrštanje; krvnogrupni antigeni

Introduction

The ABO blood group system was the first and most important human blood group system to be discovered that uses red blood cells (RBCs) and has the greatest clinical significance. The determination of ABO blood groups is the most significant test in transfusion medicine, since ABO incompatible transfusions carry the risk of inducing hemolytic transfusion reactions with potentially fatal outcomes in the recipients.

The ABO antigens are carbohydrates by their biochemical composition and are inherited as Mendelian characteristics in a codominant autosomal fashion. Three groups of genes are responsible for the formation of ABO blood group antigens: ABO, fucosyltransferase gene 1 (FUT1) and fucosyltransferase gene 2 (FUT2) [1]. The ABO genes are located on the chromosome 9 (9q34.1-q34.2), they consist of seven exons and introns, and encode specific glycosyltransferase enzymes (GTs) that attach different monosaccharides to the H substance (H antigen): N-acetyl-D-galactosamine which determines the blood group A and D-galactose which determines the blood group B [1, 2]. The FUT1, located on the chromosome 19q13.3, encodes α1,2-fucosyltransferase that catalyzes the final step in the synthesis of the H antigen (H/h, H/H), and the gene FUT2 ("secretor" gene), located in the same locus, indirectly encodes a soluble form of the H antigen (Se/se, Se/Se) which is found in bodily secretions [2, 3].

In the serum of all healthy adults with A, B and O blood groups, anti-A and/or anti-B antibodies are found almost inevitably. These antibodies are often called

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Abbreviations

ABO – ABO blood group system
RhD – Rhesus D
RBC – red blood cell
FUT – fucosyltransferase gene
GTs – glycosyltransferase enzymes
Ig – immunoglobulin
AL – acute leukemia
AML – acute myeloid leukemia

"natural" and their creation starts around the third month after contact with bacteria and viruses in the bowels that are chemically similar to A and B antigens [4]. In persons with A and B blood groups, these antibodies are primarily class M immunoglobulin (Ig), although small amounts of class G Ig are present. In persons with blood group O, the dominant class of antibodies is IgG.

The RBC antigens are hereditary characteristics and, as such, their expression is constant throughout the life of an individual. Blood type can change due to bone marrow transplant or as a result of certain types of cancers and infections. An acquired change in ABO antigen is often expressed as an acquired "B" antigen, which occurs due to the enzymatic modification of normal A_1 into an antigen similar to the B antigen, caused by bacteria, e.g. Escherichia coli, Clostridium tertium, Proteus vulgaris and Bacteroides fragilis [3]. It also appears in connection with the pathology of the gastrointestinal tract, e.g. intestinal malignancies, obstruction or severe infection/sepsis. The bacteria produce an enzyme that chemically modifies N-acetyl-D-galactosamine to D-galactosamine [3, 5]. Since the terminal sugar of the "B" antigen is galactose, the anti-B antibody will cross-react with the B-like D-galactosamine antigen. The condition is transient and resolves when the infection is cured and poses no transfusion risk other than creating a mismatch in ABO typing. Changes can also occur during malignant diseases of hematopoietic tissue. According to the literature data, changes in antigen characteristics of RBCs most often occur in acute leukemia (AL) which is characterized by clonal proliferation, accumulation of abnormal cells in the bone marrow and insufficient hematopoiesis [5].

Anemia and inclination towards bleeding and infections, conditioned by pancytopenia, are the most significant manifestations of AL [6]. Patients often need blood transfusions and blood components. The problem occurs when transfusion must be postponed because irregularities and discrepancies occur during the determination of the patient's blood group.

We are therefore describing a case of a change in the ABO antigen during an acute leukemic phase in a patient with acute myeloid leukemia (AML), in whom, after remission of the underlying disease, a recurrence of ABO antigen expression occurred.

Case Report

Due to the need for administering blood components, determination of the ABO/Rhesus (RhD) blood group type was performed in a female 27-year-old patient with the diagnosis of AML. The serological testing was performed by gel agglutination using an automated immunohematological analyzer (Diaclon ABO/D+ reverse grouping, BioRad, DiaMed-ID Micro Typing System, IH-1000). The reverse gel card showed the following results of the serum and RBCs test: anti-A negative, anti-B negative, anti-D positive, with erythrocytes A_1 negative, with erythrocytes B positive, so the result could not be interpreted due to the lack of expected agglutination. The confirmation gel card with monoclonal antibodies showed anti-A negative, anti-B negative, anti-D positive from which it could be concluded that the blood group is O RhD positive. After checking the patient's medical file, it was determined that the patient was A RhD positive.

Before new tests were performed, the possibilities of technical errors (incorrect identification of the sample/documentation, incorrect marking, incorrect results entered in the operation protocol/information system, machine/reagent errors, reading/interpretation errors) were eliminated.

After receiving a new sample, determination of the blood group was performed using the test-tube technique, where the same results were obtained. Antibody screening by using the technique of gel agglutination (ID-DiaCell Pool, IH-1000, Bio Rad) was negative. The direct antiglobulin test and auto-control were also negative. After completing the serological processing of the sample, genotyping based on the polymerase chain reaction was performed using a sequence specific primer RBC Ready Gene ABO kit (Inno-Train Diagnostik GmbH, Kronberg, Germany). By genotyping, it was confirmed that it was blood group A.

After the patient had completed the therapy and entered remission of the disease, the blood group testing was repeated. There were no discrepancies during the remission phase in determining the blood group, it was confirmed that it was an A RhD positive patient.

Discussion

Changes in RBC antigen expression are associated with malignancies, when ABO blood group antigens are most often subject to change. Van der Hart et al. described these changes in ABH antigens in malignant hematopoietic tissue diseases back in 1962, describing a very weak expression of B antigens in patients with leukemia that had normal antigen expression before the aforementioned disease [7]. As in our case, after the therapy was completed, when the disease entered the remission phase, the strength of antigen expression was restored. There are no written data in Serbia on the change of blood group in patients suffering from leukemia (except for the changes that occur during bone marrow transplantation). There have been occasional case reports in world literature about ABO blood group antigen change in malignant conditions.

Nambiar et al. reported two cases of blood group change, where one patient, 14 years of age, with an AML diagnosis, resolved the problem of determining

the blood group after successful therapy [8]. Sarwer Jahan et al. described the case of a patient who was diagnosed with AML on admission, and due to a case of anemia, after determining the blood group, received a transfusion of the blood group O. After the therapy of the underlying disease was discontinued, the blood group A was determined. The blood group A was confirmed by multiple testing and the patient continued receiving blood products of the corresponding blood group [9].

The loss of antigen expression in hematological diseases is mainly the result of mutations which affect the production of antigens in the stem cells. Therefore, in the erythrocyte progenitor arising from the changed stem cell, a complete or partial loss of antigen expression occurs. In contrast, erythrocytes that are created by stem cells which are not affected by these changes have a normal expression of erythrocyte antigens [10, 11].

It is considered that there are two mechanisms which cause changes in antigen expression. The first mechanism is the inactivation of the A and/or B transferase, which leads to the inhibition of attaching immunodominant sugar to the H antigen. At the same time, decrease in the expression of the A and B antigens occurs increasing the H antigen, because it is not converting into the A and B antigen. The literature describes that such a change in AML can be the consequence of translocation between 9 and 22 (Philadelphia) chromosomes. The gene that encodes A and B transferases is located on chromosome 9q34 [7, 12, 13].

The second mechanism is the inactivation of H transferase (coded on chromosome 19q13) that inhibits addition of L-fucose to the precursor oligosaccharide chain. Inactivation of H transferase leads to a decrease in H substance and consequently the reduction of A and B substances [14].

In many cases, loss or weakened expression of ABO antigen is associated with hematological malignant diseases, often as the first sign that points to the existence of a malignancy. Likewise, the results that indicate the return to normal expression of ABO antigen indicate a favorable treatment outcome. Antigen loss can also be seen in cancers of organs such as the stomach, colon, ovary, pancreas [15]. Unlike changes that are happening in hematological diseases, here tumors secrete large amounts of soluble A and/or B substance which neutralize the reagents for blood typing. This problem can be overcome by erythrocyte washing before determining the blood group to remove plasma that contains a soluble substance of the blood type [16].

Deviations revealed when determining the reverse and confirmation blood group must be recorded and resolved because otherwise they may lead to problems related to transfusion of blood components.

Conclusion

Changes in blood groups are rare and most often associated with hematological malignancies, although this may also occur in patients with tumors of solid organs. Changes can also happen before the diagnosis of the underlying disease is established. For this reason, it is extremely important that any discrepancy in determining the blood group is thoroughly examined to prevent transfusion of blood components of an inadequate blood type.

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PERINEAL STAPLED PROLAPSE RESECTION – A CASE REPORT

PERINEALNA STAPLERSKA RESEKCIJA PROLAPSA – PRIKAZ SLUČAJA

Dragan VASIĆ[1], Valentina ISAKOVIĆ[1], Milan SEKULIĆ[1] and Dejan IVANOV[1, 2]

Summary

Introduction. Over 100 different surgical procedures for the treatment of rectal prolapse have been described. Since these patients commonly have associated comorbidities, methods of choice include surgical techniques with a perineal approach, such as perineal stapled rectal resection. **Case Report.** A 77-year-old female patient presented with a complete rectal prolapse measuring 12 cm in length. Considering the associated comorbidities and the patient's age, perineal stapled rectal resection was chosen as the surgical modality. She underwent surgery under general anesthesia in the dorsal decubitus and slightly reverse-Trendelenburg position. The surgery lasted 35 minutes. The surgery and the immediate postoperative course were uneventful. At the follow-up examination, six months after surgery, the findings were normal, without local recurrence. There was a slight deterioration of fecal incontinence, with a Vaizey score 10/20, but the patient tolerated it well. **Discussion.** The perineal stapled rectal resection technique has fewer intraoperative complications and 6.3% fewer postoperative complications compared to classic perineal procedures (staple line bleeding, anastomotic stenosis, pelvic hematoma, sigmoid colon perforation, perirectal abscesses and rectovaginal fistulas), which were reported in many studies. However, patients with longer postoperative follow-up demonstrated a higher recurrence rate compared to patients who underwent other surgical techniques with an abdominal approach. **Conclusion.** The perineal stapled rectal resection procedure is easy to perform and acceptable for the elderly patients with associated comorbidities, who are not candidates for other surgical techniques with abdominal approach.

Key words: Rectal Prolapse; Perineum; Surgical Staplers; Recurrence; Surgical Procedures, Operative; Treatment Outcome

Sažetak

Uvod. Opisano je preko 100 različitih hirurških procedura za lečenje prolapsa rektuma. Pošto se radi uglavnom o bolesnicima sa udruženim komorbiditetima, metode izbora predstavljaju operativne tehnike sa perinealnim pristupom, kao što je i perinealna staplerska resekcija rektuma. **Prikaz slučaja.** Kod bolesnice stare 77 godina uočen je kompletan prolaps rektuma dužine 12 cm. Zbog udruženih komorbiditeta i godišta bolesnice, kao operativna tehnika izabrana je perinealna staplerska resekcija rektuma. Bolesnica je operisana u opštoj anesteziji u dorzalnom dekubitalnom i blagom anti-Trendelerburgovom položaju, ukupno trajanje operacije bilo je 35 minuta. Operacija i neposredni postoperativni tok protekli su uredno. Na kontrolnom pregledu šest meseci nakon otpusta, lokalni nalaz je uredan, bez recidiva. Došlo je do blagog pogoršanja fekalne inkontinencije, Vezlijev (*Vaizley*) skor je bio 10/20, ali bolesnica je to dobro podnela. **Diskusija.** Dokazano je u više sprovedenih studija da tehnika perinealna staplerska resekcija rektuma ima manje intraoperativnih komplikacija i sa 6,3% manje postoperativnih komplikacija u odnosu na klasične perinealne procedure (krvarenje staplerske linije, stenoza anastomoze, pelvični hematom, perforacija sigmoidnog kolona, pararektalni apcesi i rektovaginalne fistule). Međutim, u dužem postoperativnom praćenju, stopa recidiva je viša u odnosu na druge operativne tehnike sa abdominalnim pristupom. **Zaključak.** Procedura perinealne staplerske resekcije rektuma je tehnički lako izvodljiva i prihvatljiva za bolesnike starijeg životnog doba sa udruženim komorbiditetima, kod kojih nisu izbor druge operativne tehnike sa abdominalnim pristupom.

Ključne reči: prolaps rektuma; perineum; hirurški stapleri; recidivi; operativne hirurške procedure; ishod lečenja

Introduction

Patients with complete rectal prolapse are usually severe patients. They are mostly elderly patients with associated comorbidities, and surgical treatment for them carries a high risk. Therefore, surgical treatment planning must include both curative and palliative treatment options [1, 2].

Surgery is the only validated means of treating rectal prolapse. Over 100 different surgical procedures for the treatment of rectal prolapse have been described [3]. There is still no consensus on which surgical procedure is the best.

Regarding the surgical approach, procedures fall into two basic categories: transabdominal (open or laparoscopic) and perineal approach procedures [4]. The decision on the method of operative treatment should be made based on patients' comorbidities, their age, bowel function, local findings of prolapse, and the experience of the surgeon. In the elderly, high-risk patients, surgical techniques with a perineal approach are the methods of choice, although postoperatively the rate of recurrence and incontinence is higher compared to transabdominal operations [5, 6].

At the beginning of the 20th century, perineal surgeries were on the increase and became the

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Abbreviations
PSPR – perineal stapled prolapse resection

method of choice in the treatment of rectal prolapse. The most frequently performed are the Delorme and Altemeier procedures [7].

In 2007, Roland et al. described a new surgical technique called perineal stapled rectal prolapse resection (PSPR) for the treatment of complete rectal prolapse [8, 9].

Case Report

A 77-year-old female patient was admitted due to anorectal complaints and bowel prolapse. The symptoms started a few months before the examination. During the first examination, a complete rectal prolapse was established measuring 12 cm in length.

The patient denied previous abdominal surgical procedures. Her medical history included aortic valve replacement two years ago, hypothyroidism, systemic lupus erythematosus, and arterial hypertension. In the preoperative setting, the chest X-ray showed diffuse patchy changes of scar etiology on both sides in the lower lung fields. Due to uterine prolapse and urinary incontinence, she was examined by a gynecologist, who suggested separate surgical treatment. The preoperative Vaizey incontinence score was 7/20 [10].

Due to all the comorbidities and the age of the patient, PSPR was chosen as the operative technique, primarily due to minimal surgical trauma and based on literature data showing good results compared to transabdominal procedures.

The patient underwent surgery under general anesthesia in the dorsal decubitus and slightly reverse-Trendelenburg position **(Figure 1)**. The prolapse was

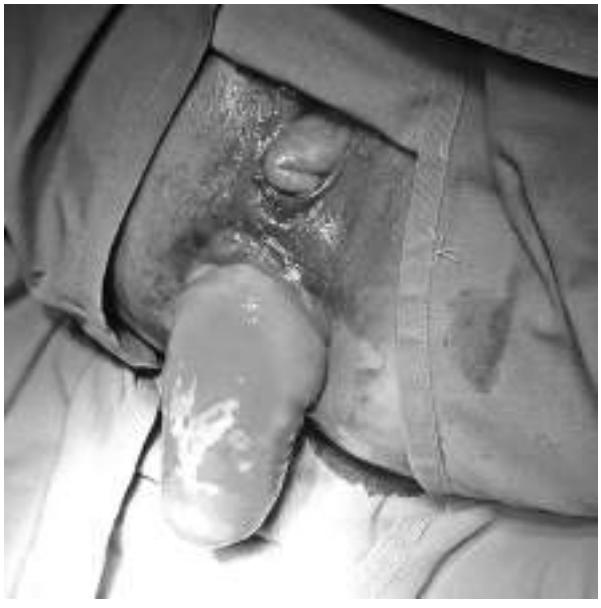

Figure 1. Complete rectal prolapse measuring 12 cm in length
Slika 1. *Prolaps rektuma u dužini od 12 cm*

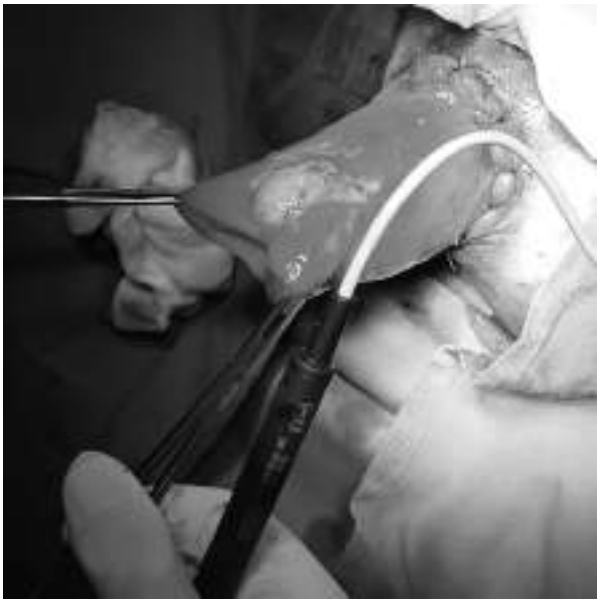

Figure 2. Placement of fixation sutures
Slika 2*. Postavljanje fiksacionih šavova*

completely retracted by a grasper, and then its distal part was fixed with 10 single absorbable (3.0) sutures **(Figure 2)**. After that, at 6 and 12 o'clock position, an incision was made and transection of the prolapse was done using two linear staplers **(Figure 3)**. After that, the prolapse was resected using two Contour staplers. The stapler line was sutured with an extended absorbable suture (3.0) **(Figure 4)**. Hemostasis was correct, intraoperative loss was approximately 100 ml of hemorrhagic fluid. The total duration of the procedure was 35 minutes. In the immediate postoperative course, the function of the anal sphincter was preserved. Per os intake (liquid) was introduced 6 hours after surgery.

Figure 3. Transection using a linear stapler
Slika 3. *Transekcija pomoću linearnog staplera*

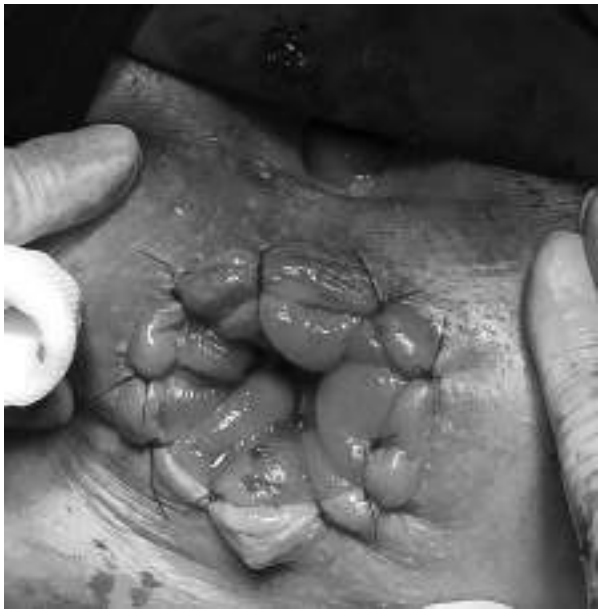

Figure 4. Condition after resection
Slika 4. *Stanje nakon resekcije*

The further postsurgical course was uneventful. On the first postsurgical day, there was no blood in the patient's stool. On the second and fourth postoperative days, rectoscopy was performed showing a neat staple line of the entire circumference 2 cm from the anocutaneous border. The patient was discharged on the fifth postoperative day for further home treatment.

The histopathological findings of the resected part of the rectum showed that it was a non-specific chronic colitis without signs of neoplastic proliferation.

At a follow-up examination six months after surgery, the local findings were normal, with no recurrence. There was a slight deterioration of fecal incontinence, Vaizey score 10/20, but the patient handled it well. The patient is completely satisfied with the cosmetic outcome.

Discussion

Over 100 different surgical procedures have been described for the treatment of rectal prolapse [11]. Perineal stapler resection of the rectum using a Contour stapler is an alternative to the conventional transanal (perineal) Rehn-Delorme [12] and Altemeier procedures [13]. The safety of the PSPR technique was reported by Hetzer et al. in his study including 32 patients, without intrasurgical complications, and with 6.3% fewer postsurgical complications in comparison to the classic perineal procedure (staple line bleeding, anastomosis stenosis, pelvic hematoma, perforation of the sigmoid colon, pararectal abscesses, and rectovaginal fistulas) [14, 15]. In order to prevent injury to the Douglas cord, or possibly an associated enterocele, as in our patient, it is necessary to place the patient in the dorsal decubitus and anti-Trendelenburg position.

The study including 408 patients undergoing PSPR by Fan et al. showed that the most common complication was staple line bleeding, and the total complication rate was 14.5% (51/350) [16].

A modification of the surgical technique is also possible, when transection of the prolapse is performed using linear staplers instead of using two Contour staplers. An important aspect of this procedure is that the number of stapler charges for bowel resection is not even. It depends on the length and thickness of the prolapsed rectum [17]. Since the resection site between the staples is a weak point and a potential complication location, it is necessary to reinforce the staple line with individual absorbable sutures.

There are four studies with relatively short postoperative follow-ups (from 1 - 6 months), which have shown significant improvement in constipation and continence after PSPR surgery. However, like in our case, postoperative deterioration of fecal incontinence was also described in other studies. The most probable cause is the shortening of the rectal reservoir [18, 19].

In the study by Tschuor et al., with an average postoperative follow-up of 40 months (14 - 58 months), the recurrence rate was 44% [20]. There are several reasons that may cause a higher recurrence rate compared to other non-operative techniques with a perineal approach (44% versus 32%).

One of the reasons is most likely the selection of patients (PSPR is the method of choice for severe patients with numerous comorbidities). Also, these patients most often have pelvic floor insufficiency, and the surgical technique does not include levatoroplasty. In all the mentioned studies, the length of prolapse was greater than 7.5 cm, which is higher than the average length of prolapse reported in classical operative techniques, showing that these patients also have a greater dysfunction. In the end, one must take into account the surgical training, as it is a relatively new and rarely used technique so it may be an additional factor.

Recommendations published in a recent consensus study state that PSPR is a viable surgical option for selected patients, especially the elderly and polymorbid patients with shorter life expectancy [21].

These recommendations confirm the findings of the aforementioned studies; PSPR has less intraoperative and immediate postoperative morbidity, but a higher rate of recurrence in the longer postoperative follow-up.

Based on the materials used, PSPR represents a more expensive operative technique compared to classic procedures (Delorme or Altemeier). However, shorter duration of surgery and shorter hospital stay compensate for the difference in price.

Conclusion

Perineal stapler rectal resection is a safe surgical technique for the treatment of rectal prolapse. It includes resection of the prolapsed part without the need for mobilization or dissection of the rectum.

As shown in our case, this procedure is technically easy to perform and acceptable for elderly patients with associated comorbidities, who are not candidates for other surgical techniques with abdominal approach.

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PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA – DILEMMAS IN DIAGNOSIS AND CHOICE OF THERAPY – A CASE REPORT

PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA – DILEME U DIJAGNOZI I IZBORU TERAPIJE – PRIKAZ SLUČAJA

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Summary

Introduction. Pityriasis lichenoides et varioliformis acuta is a rare inflammatory skin disease of unknown etiology and its diagnosis is sometimes established by eliminating diseases that are considered in the differential diagnosis. Given the lack of randomized clinical trials, recommendations for therapy remain based on case reports and case series. **Case Report.** We present a 63-year-old female patient with generalized skin lesions including, papules, papulonecrotic lesions, and atrophic scars accompanied by a subjective feeling of itching that occurred 2 months before admission. The histopathological findings showed a mixed perivascular inflammatory cellular infiltrate and capillary blood vessels with thickened walls in the superficial part of the dermis as signs of vasculitis. The infiltrate was dominated by lymphocytes, neutrophils were admixed, but there were no signs of cellular atypia, which supported the clinical diagnosis of pityriasis lichenoides et varioliformis acuta. Therapy with systemic corticosteroids and doxycycline was applied, which led to the resolution of lesions. **Conclusion.** The authors would like to bring to the readers' attention a rare skin disease, pityriasis lichenoides et varioliformis acuta, point to papulonecrotic tuberculids in differential diagnosis due to similar clinical presentation, remind them of the dilemmas that may arise in case of the described lymphocytic vasculitis based on the findings of histopathological analysis, and highlight the effectiveness of doxycycline and prednisone in the therapy.

Key words: Pityriasis Lichenoides; Skin Diseases; Diagnosis, Differential; Prednisolone; Doxycycline

Sažetak

Uvod. *Pityriasis Lichenoides et Varioliformis Acuta* je retko inflamatorno oboljenje kože nerazjašnjene etiologije čija se dijagnoza ponekad postavlja eliminacinom oboljenja koja diferencijalnodijagnostički dolaze u obzir. S obzirom na nedostatak randomizovanih kliničkih studija, preporuke za terapiju ostaju bazirane na prikazima i serijama slučaja. **Prikaz slučaja.** Prikazujemo bolesnicu starosti 63 godine sa generalizovanim promenama na koži u vidu papula, papulonekrotičnih lezija i atrofičnih ožiljaka praćenih subjektivnim osećajem svraba koje su se javile dva meseca pred hospitalizaciju. Na histopatološkom nalazu su opisani perivaskularno smešten mešoviti zapaljenski infiltrat i kapilarni krvni sudovi zadebljalog zida u superficijalnom delu dermisa kao znaci vaskulitisa. U infiltratu su dominirali limfociti uz prisustvo i neutrofila ali znaci atipije ćelija nisu opisani što je ukazivalo na klinički postavljenu dijagnozu *Pityriasis Lichenoides et Varioliformis Acuta*. Primenjena je terapija sistemskim kortikosteroidima i doksiciklinom što je dovelo do rezolucije promena. **Zaključak.** Autori žele da podsete na *Pityriasis Lichenoides et Varioliformis Acuta* kao retko kožno oboljenje, diferencijalnodijagnostički navedu i papulonekrotične tuberkulide zbog slične kliničke prezentacije, podsete na dilemu koja se može javiti u slučaju opisanog limfocitnog vaskulitisa na nalazu histopatološke analize i navedu efikasnost doksiciklina i prednizona u terapiji.

Ključne reči: Pityriasis Lichenoides; kožne bolesti; diferencijalna dijagnoza; prednizon; doksiciklin

Introduction

Pityriasis lichenoides is an uncommon inflammatory skin disease representing a spectrum of diseases that manifest in two forms: pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC). The incidence and prevalence of PLEVA have not been precisely determined; it occurs at all ages, most often in the second and third decade of life, while it is described in children in about 20% of cases [1, 2]. The etiology of the disease is not fully elucidated and attempts are made to explain it by an inflammatory reaction triggered by infectious agents, a secondary inflammatory response to T-cell dyscrasia or hypersensitivity mediated by immune compex, while some argue that it is a T-cell lymphoproliferative disease [1, 3].

Due to the rarity of this disease and a long list of diseases included in the differential diagnosis, establishing the diagnosis is difficult and sometimes it is made by exclusion of diseases by differential diagnosis [4]. Therapy recommendations are often debated because they are based on case reports and case series,

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Abbreviations
PLEVA – pityriasis lichenoides et varioliformis acuta
PLC – pityriasis lichenoides chronica
LyP – lymphomatoid papulosis

primarily due to the self-limiting course of the disease and the consequent lack of randomized clinical trials [1]. The aim of this paper was to point to this rare entity which is often associated with dilemmas in establishing the diagnosis and choice of treatment modality.

Case Report

We hereby present a 63-year-old female patient who was hospitalized due to generalized skin lesions including papules, papulonecrotic lesions, and atrophic scars accompanied by a subjective feeling of itching. The eruptions appeared 2 months before admission, first on the skin of the front abdominal wall, followed by changes on the trunk and lower extremities, and the upper extremities and capillitium. The skin changes occurred in bursts and some resolved with atrophic and varioliform scars. The patient denied occasional medication intake and there was no apparent episode of any infection before the onset of the eruptions. She presented with arterial hypertension and diabetes, which were well controlled.

On admission, the patient was in good general condition, cardiopulmonary compensated and afebrile,

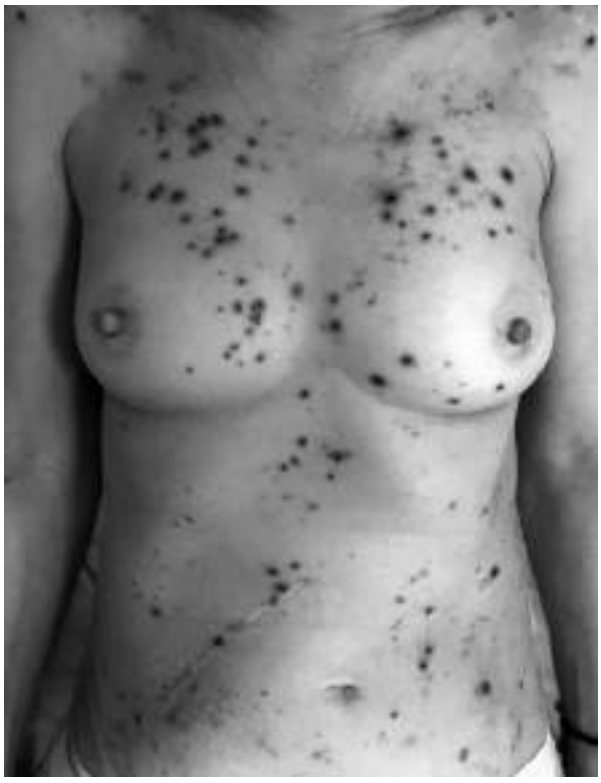

Figure 1. Polymorphic clinical presentation, anterior side of the trunk
Slika 1. *Polimorfna klinička prezentacija, prednja strana trupa*

Figure 2. Skin eruption consisting of livid erythematous papules, some of which are covered with necrotic eschar or central sanguinolent crusts, posterior side of the trunk
Slika 2. *Kožne promene u vidu lividno eritematoznih papula, od kojih su neke prekrivene nekrotičnom esharom ili centralnom sangvinolentnom krustom, zadnja strana trupa*

without adenopathy or other clinical signs on physical examination. Numerous erythematous livid papules with a diameter of several millimetres to 1 cm were present on the trunk and lower extremities, some of which were covered with necrotic eschar or with central sanguinolent crusts **(Figures 1 and 2)**. Individual changes of similar characteristics were present on the skin of the upper extremities and capillitium, while the skin of the face, palms and soles as well as visible mucous membranes were spared. Individual atrophic and varioliform scars up to 1 cm in diameter were registered on the skin of the pretibial area of lower legs, on both sides **(Figure 3)**.

Laboratory tests, including a full blood cell count with differential, markers of inflammation, liver and kidney function tests, urine, serum protein electrophoresis, immunoglobulins G, M and A, C3 and C4 complement components, antinuclear antibodies to primate liver and Hep-2 cells, beta-2 microglobulin, Treponema pallidum serology (venereal disease research laboratory, Treponema pallidum hemagglutination) as well as the QuantiFERON-TB Gold test, were within reference values or negative. X-ray of the lungs and heart as well as ultrasonography of the upper abdomen showed no pathological changes.

The histopathological findings showed a diffusely hyperkeratotic epidermis with flattened rete ridges and focal necrosis of the papillary dermis. The

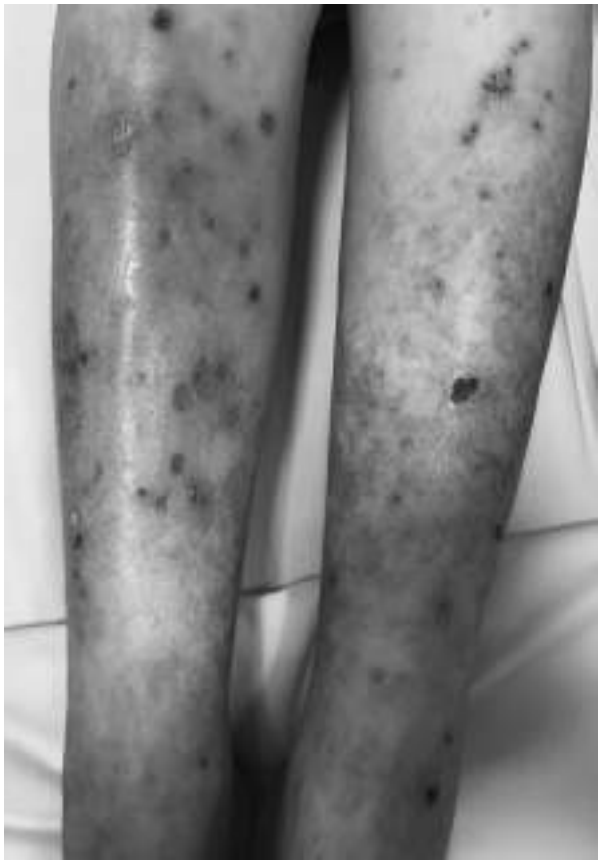

Figure 3. Atrophic and varioliform scars, postinflammatory hyperpigmented macules and ulceronecrotic lesions, pretibial area of lower legs
Slika 3. *Atrofični i varioliformni ožiljci, postinflamatorne hiperpigmentovane makule i ulceronekrotične lezije, pretibijalna regija potkolenica*

epidermis showed ulcerations and crusts on the surface. In addition, both moderately dense mixed perivascular inflammatory cellular infiltrate and capillary blood vessels with thickened walls were described in the superficial part of the dermis as signs of vasculitis. The infiltrate was dominated by lymphocytes, neutrophils were admixed, but there were no signs of cellular atypia, which indicated the clinical diagnosis of PLEVA **(Figure 4)**.

Systemic corticosteroid (oral prednisone at a dose of 0.5 mg/kg), antihistamine and antibiotic therapy (cephalexin) was prescribed based on the antibiogram, considering that Staphylococcus aureus was isolated from the swab of the skin lesions. Upon completion of antibiotic therapy with cephalexin in the duration of 10 days, doxycycline was prescribed at a daily dose of 100 mg for 2 weeks, with further gradual reduction of the dose of corticosteroids for a month until withdrawal, which resulted in regression of skin lesions within 3 months, with post-inflammatory hyperpigmented macules and individual varioliform scars. In addition, the total duration of the disease was 7 months without recurrence in the follow-up period of one year.

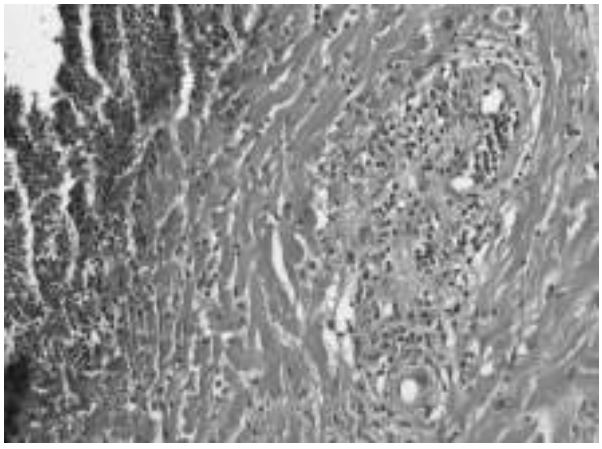

Figure 4. Histopathological finding of the lesion showing necrosis of the epidermis and papillary dermis with ulceration and crust on the surface and mixed perivascular inflammatory cellular infiltrate with signs of vasculitis; The infiltrating cells show no signs of atypia; HE x 200
Slika 4. *Histopatološki nalaz lezije pokazuje nekrozu epidermisa i papilarnog dermisa sa ulceracijom i krustom na površini kao i mešoviti perivaskularno smešten inflamatorni infiltrat sa znacima vaskulitisa. U infiltratu nema znakova atipije ćelija. HE, x 200*

Discussion

Clinical manifestations of PLEVA include eruptions of erythematous macules with rapid progression into inflammatory papules with pityriaziform desquamation. In further progression, the scale thickens and remains present centrally while separating on the periphery of papules that may undergo necrosis with the consequent appearance of centrally located ulcerations or evolve into PLC lesions. It is characterized by recurrent crops of skin lesions and the consequent polymorphic clinical picture, as well as sequelae in the form of post-inflammatory hypo- or hyperpigmented macules and varioliform scars, which was also the case in our patient [5]. The distribution of lesions is most often central in the area of the trunk and flexor surfaces of the proximal extremities, but other types of distribution, such as peripheral or diffuse, may be seen as in our patient, which prompted us to consider other differential diagnoses [1].

The list of diseases included in the differential diagnosis described in the literature is extensive and includes: lymphomatoid papulosis, cutaneous vasculitis, arthropod bite reactions, disseminated herpes simplex virus infection or varicella zoster virus infection, Gianotti-Crosti syndrome, erythema multiforme, pityriasis rosea, psoriasis guttata, secondary syphilis, pityriasis lichenoides-like mycosis fungoides, polymorphic light reaction, lichen planus, exanthematic eruptions to drugs, etc. [4, 6–8]. We included lymphomatoid papulosis (LyP) and cutaneous vasculitis into differential diagnosis, which is in compliance with literature data, but also tuberculosis papulonecrotica cutis, i.e. papulonecrotic tuberculides, which the authors did not notice in the differential diagnosis when reviewing the avail-

able literature on PLEVA. However, a review article from 2022 included PLEVA in the differential diagnosis for papulonecrotic tuberculides, due to a similar clinical presentation [9]. During the diagnostic processing of our patient, a heart and lung X-ray, QuantiFERON-TB Gold test and skin biopsy were performed in order to rule out the granulomatous nature of the disease.

The diagnosis of PLEVA is made based on medical history, physical examination and skin biopsy for histopathological analysis, which is of great use when differentiating it from other skin diseases with similar clinical presentation [10]. The histopathological findings in LyP include a wedge-shaped or perivascular dermal infiltrate of pleomorphic lymphoid cells that resemble Reed Sternberg cells, as well as epidermal necrosis with the presence of ulceration, thus ruling out this disease in our patient. Differentiating PLEVA from LyP is of key importance considering the different prognosis of the disease and the significant risk of malignant transformation of LyP into cutaneous lymphoma. In case of a diagnostic dilemma, immunohistochemical staining is important, which was not necessary in our case. In PLEVA, CD8+ T-cells are dominant, which speaks in favour of the diagnosis, while the presence of atypical CD30+ cells excludes it and indicates LyP [4, 11, 12]. In PLEVA, perivascular and diffuse infiltrates of lymphocytes and histiocytes are described, i.e. superficial perivascular interface dermatitis, which at first resembles lymphocytic vasculitis and may lead to a diagnostic dilemma, also present in our case. However, unlike cutaneous vasculitis, true fibrinoid necrosis of blood vessels is absent in PLEVA [2, 4]. It is important to emphasize the importance of feedback and communication with pathologists in order to establish adequate diagnosis of the disease.

Bearing in mind the unclear etiology of the disease, PLEVA therapy is still a subject of discussion. Given the tendency of the disease towards spontaneous resolution, the evaluation of therapeutic modalities is limited due to the lack of adequate control groups and the impossibility of conducting randomized prospective studies [6]. Recommendations remain based on retrospective studies as well as case reports and case series that generally recommend antibiotics and/or phototherapy as effective therapeutic modalities, with corticosteroids as adjunctive therapy in severe cases of PLEVA [7]. Antibiotics with anti-inflammatory properties, such as tetracycline in adults and erythromycin in children, are most often prescribed until the skin lesions are in complete remission, usually up to 3 months [13, 14]. A review article from 2019 on PLEVA in adults by Bellinato et al., suggested the use of methotrexate or erythromycin with or without topical corticosteroids as the first therapeutic option, but in our case, therapy with doxycycline and systemic corticosteroids resulted in a positive therapeutic response without the need for the use of methotrexate [13]. In refractory cases, in addition to methotrexate, successful therapy with acitretin, dapsone and cyclosporine is described in the literature [15, 16].

Gelmetti et al. assumed that the distribution of lesions is of importance in predicting the course of the disease, and that patients with a diffuse distribution of lesions had the shortest average course of the disease (11.4 months), while those with a peripheral distribution, the longest (31.3 months). In case of patients with the central distribution, it was associated with an intermediate duration of the disease (17.3 months) [17]. These data are not in accordance with some recent publications such as the research conducted by Ersoy-Evans et al. in which the median duration for the diffuse form of the disease was 22 months and 12 months for the central and peripheral forms [18]. In our case of diffuse distribution, complete resolution occurred within 7 months.

Conclusion

In conclusion, we would like to bring to the readers' attention a rare skin disease, pityriasis lichenoides et varioliformis acuta, which is often associated with dilemmas in establishing the diagnosis and deciding on the choice of therapy. The differential diagnosis includes papulonecrotic tuberculides, due to similar clinical manifestations with the diffuse form of pityriasis lichenoides et varioliformis acuta. Also, we wish to point out the dilemma that can occur in the case of described lymphocytic vasculitis when interpreting the findings of histopathological analysis. Unlike in cutaneous vasculitis, there is no true damage to blood vessels with fibrinoid necrosis in pityriasis lichenoides et varioliformis acuta. The use of doxycycline and prednisone was effective in our patient, but spontaneous resolution of the lesions cannot be ruled out either.

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Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

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∗ Disertacija

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Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

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CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

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Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.