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ММР

Original article

ATG IN CONDITIONING FOR ALLOGENEIC HSCT IN AML PATIENTS

АНТИ-ТИМОЦИТЕН ГЛОБУЛИН ВО КОНДИЦИОНИРАЊЕ ЗА АЛОГЕНА ТХМК КАЈ ПАЦИЕНТИ СО АМЛ

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Abstract

Introduction. Acute myeloid leukemia (AML) is a malignant hematological disease characterized by accumulation of malignant hematopoietic immature precursors in the bone marrow, resulting in failure of the marrow. Timely diagnosis and treatment are of the highest importance because of the acute course of the disease and the mortality rates that are unacceptable, especially if the disease is misdiagnosed or left untreated. Allogeneic hematopoietic stem cell transplant (HSCT) is the treatment with the biggest curative potential and must be included in post-remission treatment of patients with AML. Up to 70% of patients undergoing allogeneic HSCT will suffer graft versus host disease (GvHD) to some extent, acute or chronic, significantly contributing to the mortality rates. One of the options of GvHD prophylaxis is to do *in vivo* T cell depletion by application of anti-thymocyte globulin (ATG) during conditioning.
Methods. In our study we analyzed 40 patients with AML diagnosed and treated in the University Clinic for Hematology in Skopje in the period between 2014 and 2021. The median age of patients was 40.9 years. As far as the conditioning, we used myeloablative conditioning (MAC) in almost all patients (38 patients – 98%). ATG was administered on days -3-2-1 before transplant in 19 patients (47%). We made a comparative analysis of the GvHD rates, infectious complications rates and survival rates in patients receiving and not receiving ATG in conditioning.
Results. In the ATG group, 15.8% of patients were diagnosed with acute GvHD, and the same percentage accounted for the chronic GvHD. The non-ATG group had significantly higher rates of acute GvHD (29%) and chronic GvHD (24%). No inferiority was confirmed regarding fatal infectious rates in the ATG group compared to the non-ATG group. The same accounted for the relapse rates (in the non-ATG group (19%) compared to the ATG group (16%)). This analysis concludes that ATG in conditioning of patients with AML undergoing allogeneic HSCT as a method of *in vivo* T cell depletion is a justified therapeutic approach contributing to treatment benefits to the patients.

Keywords: acute myeloid leukemia, anti-thymocyte globulin, allogeneic hematopoietic stem cell transplantation, relapse

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Апстракт

Вовед. Акутната миелоидна леукемија (АМЛ), претставува малигно хематолошко заболување кое се одликува со акумулација на малигни хематопоетски незрели прекурзори во коскената срцевина резултирајќи со нејзина инсуфициенција. Навременото дијагностицирање и третман претставува императив кај ова заболување, кое се одликува со акутен тек и високи стапки на морталитет кои се неприфатливи, особено ако дијагнозата е задоцнета или не се започне со лекување кај пациентот. Алогената трансплантација на хематопоетски матични клетки (ТХМК) претставува тераписка опција која се одликува со најголем куративен потенцијал во лекување на пациентите со АМЛ и потребно е да биде вклучена во лекување на пациентите. Според одредени податоци, дури кај 70% од пациентите кај кои е реализирана алогена ТХМК може да биде нотирана одредена форма на акутна или хронична форма на болест на графтот против домаќинот (Graft versus host disease-GvHD). Потешките форми на GvHD имаат сигнификантен придонес во стапките на морталитет асоцирна со трансплантацијата. Една од можностите да се направи профилакса на GvHD е да се изврши in vivo Т клеточна деплеција со примена на анти-тимоцитен глобулин (АТГ) во кондиционирањето на пациентите пред апликација на графтот.
Методи. Извршивме евалуација на 40 пациенти со АМЛ, дијагностицирани и лекувани на клиниката за Хематологија во Скопје и кај кои е реализирана алогена ТХМК во периодот од 2014 до 2021 година. Средната возраст на пациентите изнесуваше 40.9 години. Кај 38 (95%) пациенти беа ординирани миелоаблативни протоколи на кондиционирање. АТГ беше ординиран на ден -3,-2,-1 пред апликацијата на

графтот, кај 19 паациенти (47%). Направена беше компаративна анализа на стапките на релапс, стапките на инфективни компликации и преживување кај пациентите кои примиле АТГ и групата на пациенти каде не е ординиран АТГ.
Резултати. Стапката на акутен и хроничен GvHD кај пациентите кај кои беше ординиран АТГ изнесуваше 15.8% за двете групи, и е сигнификантно пониска во однос на стапката на акутен и хроничен GvHD кај пациентите кај кои не е ординиран АТГ и изнесуваше 29 % и 24% соодветно. Не беше потврдена инфериорност во однос на фаталните инфективни компликации кај пациентите со ординиран АТГ, ниту во однос на стапките на релапс (19% кај пациентите без АТГ и 15.7% кај пациентите со АТГ). Оваа ретроспективна анализа покажува позитивно искуство и ја оправдува примената на АТГ во кондиционирање кај пациентите со АМЛ каде се реализира алогена ТХМК.

Клучни зборови: Акутна миелоидна леукемија; Анти-тимоцитен глобулин, алогена трансплантација на хематопоетски матични клетки, релапс

Introduction

Acute myeloid leukemia (AML) is a malignant hematological disease characterized by accumulation of malignant hematopoietic immature precursors in the bone marrow, resulting in failure of the marrow [1]. Timely diagnosis and treatment are of the highest importance because of the acute course of the disease and the mortality rates that are unacceptable, especially if the disease is misdiagnosed or left untreated. The incidence is age dependent, and it is in the range of 1 case in 100,000 until the age of 25, and rises to 25 cases per 100,000 persons after the age of 65-70, which represents an exponential rise in the incidence rates [2]. The median age at diagnosis is 70 years, and the incidence rate varies between 3-4 cases per 100,000. The symptoms of the disease are often nonspecific, and the diagnosis is suspected based on a simple blood count analysis. To confirm the diagnosis further and more specific laboratory tests are needed. To establish the right treatment, course and define the risk profile of the patient it is necessary to classify the patient in one of the risk groups based on cytogenetic abnormalities and aberrations in NPM1, FLT3, CEBPA, ASXL1, TP53 genes [3]. The treatment of patients categorized in the favorable risk group, based on chemotherapy regimens, results in complete remission (CR) rates between 70 and 90%, and survival rates of around 60%, but the survival rates of patients in the intermediate risk group and adverse risk group are unsatisfactory and can be found in the range of a five-year survival of about 35% in patients under 60 years old and 10% in patients over 60 years old (4). That is why allogeneic hematopoietic stem cell transplant (HSCT) as a treatment with the biggest curative potential must be included in post-remission treatment of patients with AML. It is indicated in patients with favorable risk, but positive MRD (minimal residual disease), and in patients with intermediate and adverse risk profile, regardless of MRD. To be more precise, a risk-adopted approach of post-remission treatment of patients with AML should include assessment of transplant-related mortality (TRM) risk, leukemia risk characteristics and MRD [5,6]. Up to 70% of patients undergoing allogeneic HSCT will suffer graft versus host disease (GvHD) to some extent, acute or chronic, contributing to the mortality rates. It is the most life-threatening complication, developed by T cells from the donor, recognizing the host as foreign. One of the options of GvHD prophylaxis is to do *in vivo* T cell depletion by application of anti-thymocyte globulin (ATG) during conditioning [7]. The posttransplant immunosuppression is standard, as calcineurin inhibitors (CNI) + methotrexate for myeloablative conditioning, and cyclosporin A + mycophenolate mofetil for reduced intensity conditioning. Herein, we will demonstrate the justified use of ATG in conditioning for reduction of GvHD rates and better quality of life without worsening overall survival of the patients. The major drawback is the fear of increased rates of infectious complications, mainly reactivation of Epstein-Barr virus (EBV) and cytomegalovirus (CMV), and fatal fungal infections that will not result in improved TRM and overall survival (OS) [8]. Also, there are studies confirming the ,,fear'' that the use of ATG worsens relapse rates, even in patients receiving myeloablative conditioning [9,10].

Materials and methods

We analyzed 40 patients with AML, diagnosed and treated in the University Clinic for Hematology in Skopje. The treatment consisted of a standard induction chemotherapy 7+3 (antimetabolite cytosine arabinoside (Ara-C) and 3 days of an anthracycline (i.e., daunorubicin or idarubicin)) [11]. If CR was not achieved after standard induction, confirmed with reevaluation of bone marrow after standard induction therapy, we continued with FLAG-Ida regimen (fludarabine 30 mg/m2, AraC 2 g/m2 for 5 days, idarubicin 10 mg/m2 for 3 days, and G-CSF 5 micro g/kg from day 0 until neutrophil recovery) and if CR was achieved the patient was considered a candidate for hematopoietic stem cell transplantation (HSCT) as mandatory further treatment of the disease. If CR was confirmed after standard induction, a course of high dose ARA-C was administered as consolidation therapy before allogeneic HST. All patients before HSCT were in CR. We performed both related and unrelated matched allogeneic HSCT, and haploidentical HST in 5 patients. We analyzed the infection rates and outcome in patients re-

ceiving ATG in conditioning *vs.* those not receiving ATG. All our patients were on standard fungal prophylaxis with fluconazole 200 mg, and ciprofloxacin 500mg twice daily for gastrointestinal decontamination. The same referred for GvHD rates, relapse rates and outcome in these two groups of patients. We used a standard dose of ATG -thymoglobuline at 5 to 10 mg/kg. Some of the decisions on the dose were made based on the information of the donor (for example, when we used female donors, especially females giving previous births, information on permissive mismatch in the high-resolution HLA typing, in matched unrelated donors, etc). The interval between ATG and the infusion of the allograft was debated, but we sticked to the rule - the closer to transplant, the higher the levels of circulating ATG which led to better GVHD protection [12,13]. Usually, ATG was administered on days -3-2-1 before transplant.

Results

In our study we analyzed 40 patients with AML diagnosed and treated in the University Clinic for Hematology in Skopje in the period between 2014 and 2021. Of the analyzed group, 18 (45%) were females and 22 (55%) were males (Figure 1).

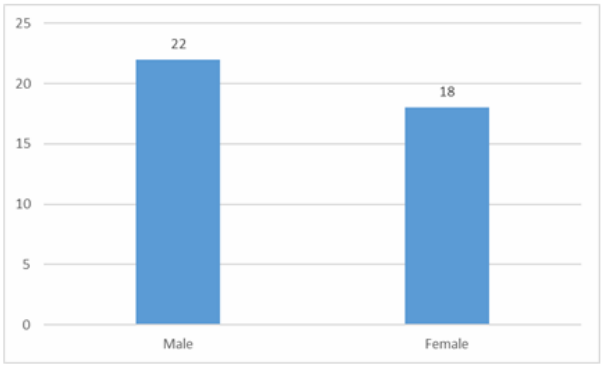

Fig. 1. Sex distribution

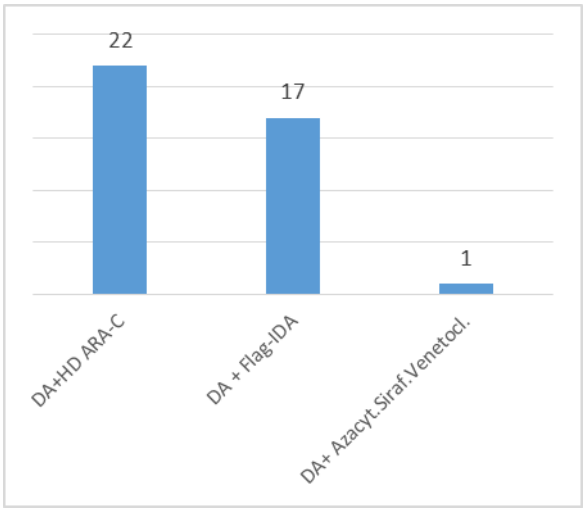

Fig. 2. Treatment before allogeneic HSCT

The median age of patients was 40.9 years, ranging from 16 years as our youngest patient to 65 years, being our oldest patient. All our patients were treated with a standard induction therapy (7+3). With this therapy we managed to achieve CR in 22 patients (45%) and continued with consolidation therapy with HD ARA-C. In those that were not in CR we continued with re-induction or second line treatment using FLAG-Ida regimen (42.5%). Only in one patient we used a combination of azacytidine, venetoclax and sorafenib (2.5%) (Figure 2).

In 10 (55%) of the remaining 18 patients, CR was not established after the standard induction therapy, suggesting a worse risk profile. All patients before allogeneic HSCT were in CR confirmed by analysis of the bone marrow using a standard cytomorphology as well as flowcytometry. In 22 patients we could do cytogenetics to define the risk profile. The majority (19 patients, 86.35%) was in the intermediate and poor risk profile (Figure 3). In almost all of these patients we had to do the therapy intensification in order to achieve CR and proceed to allogeneic HSCT.

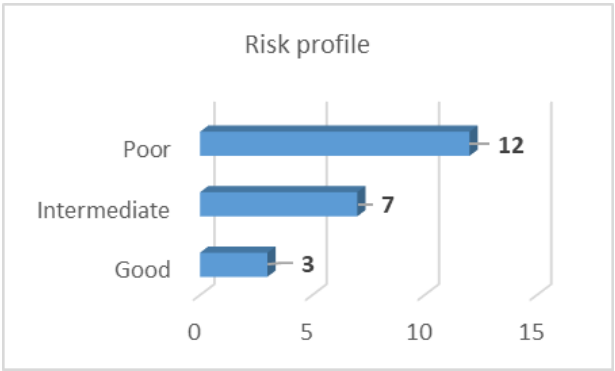

Fig. 3. Risk assessment of the disease

The median time to performing allogeneic PBSCT was 6.6 months. All of our patients received hematopoietic stem cells from peripheral blood (PBSC), so the source of allograft as variable influencing rates of GvHD was excluded. There are data showing that the usage of PBSC as allograft could lead to higher rates of detected GvHD, especially chronic GvHD [14].

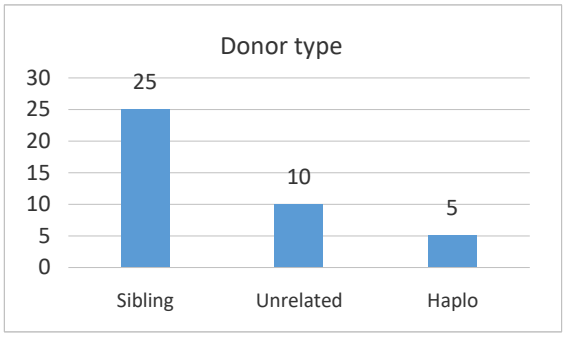

Fig. 4. Type of donor for allogeneic HSCT

In our group of patients, we used sibling donors in 25 (62.5%), unrelated donors in 10, and haploidentical donors in 5 patients (Figure 4).As far as the conditioning, we used myeloablative conditioning (MAC) in almost all patients. Only in 2 patients we used reduced intensity conditioning (Figure 5).

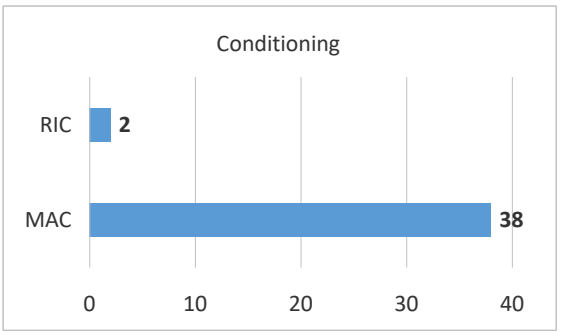

Fig. 5. Conditioning intensity for allogeneic HSCT

If we analyze the type of conditioning, Bu-Cy regimen (Busulfan + Cyclophosphamide) predominated, and adding melphalan (Bu-Cy-Mel) created the second most used conditioning regimen. Other regimens used were thiotepa-busulfan-fludarabine and busulfan-fludarabine (Figure 6).

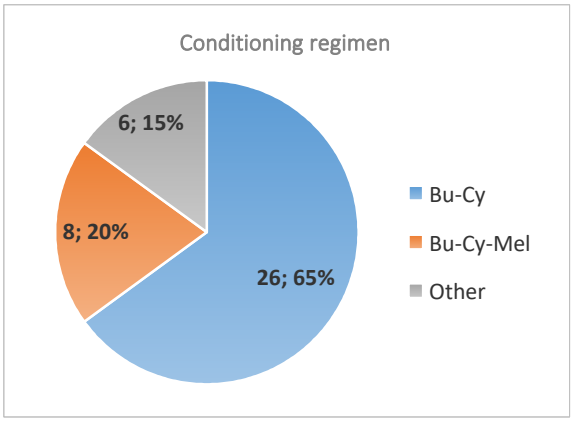

Fig. 6. Type of conditioning regimen for allogeneic HSCT

ATG was added to the conditioning regimen in 19 patients (Figure 7). We used rabbit ATG formulation. A standard premedication was administered using methylprednisolone, acetaminophen, chloropyramine, loratadine. We did not register adverse events, nor serious adverse events that would result in withdrawing the ATG. There were only some febrile episodes that were easily managed. The dose used was in the range of 5-10 mg/kg body weight depending on the donor type and type of HSCT.

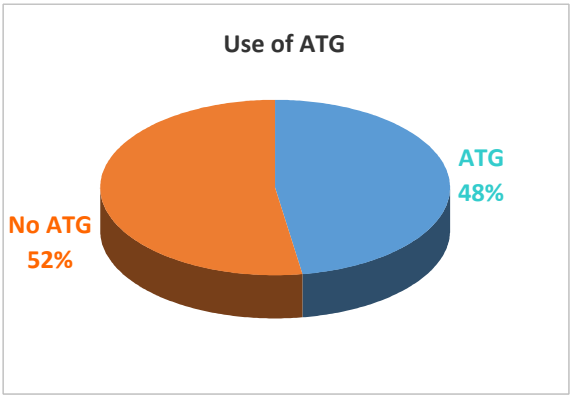

Fig. 7. Use of ATG in conditioning

We compared the rates of GvHD in these two groups of patients. In the ATG group, in 3 patients (15.8%) acute GvHD was diagnosed, and also 3 patients (15.8%) were diagnosed with chronic GvHD. One patient had acute GvHD grade I-II, and 2 patients (10%) acute GvHD grade III-IV (Figure 8).
In the non-ATG group, acute GvHD was diagnosed in 6 patients (29%), and 5 patients (24%) were diagnosed with chronic GvHD. Two patients had acute GvHD grade I-II, and 4 patients (19%) acute GvHD grade III-IV(Figure 9).

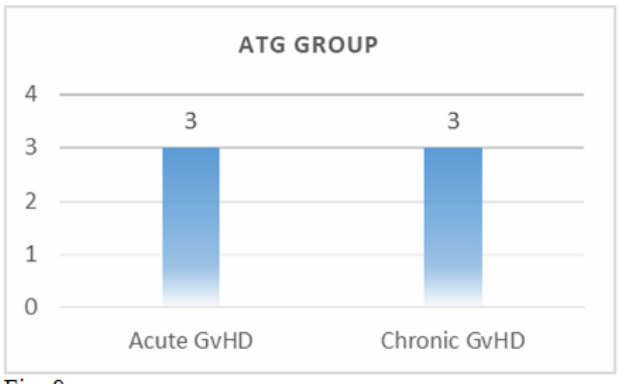

Fig. 8a.

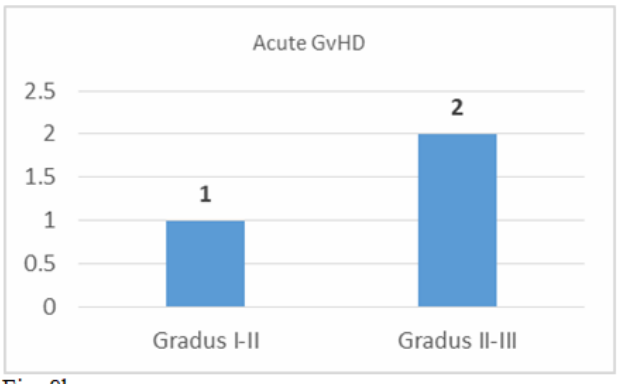

Fig. 8b.

Fig. 8. Acute GvHD intensity in patients with ATG conditioning

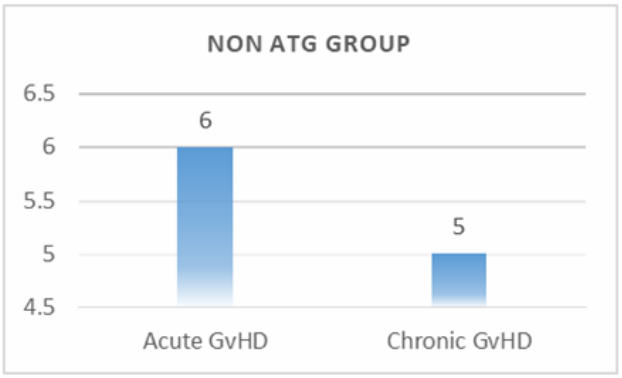

Fig. 9a.

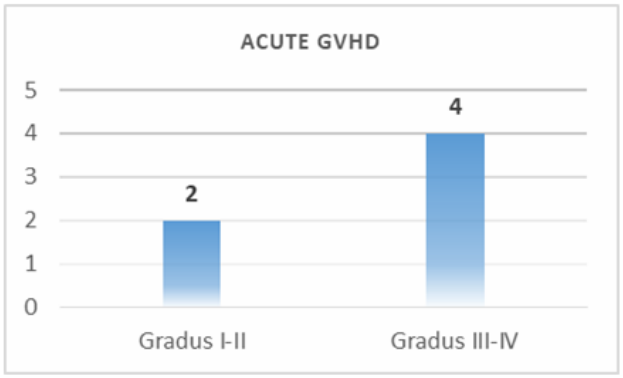

Fig. 9b.

Fig. 9. Acute GvHD intensity in patients without ATG conditioning

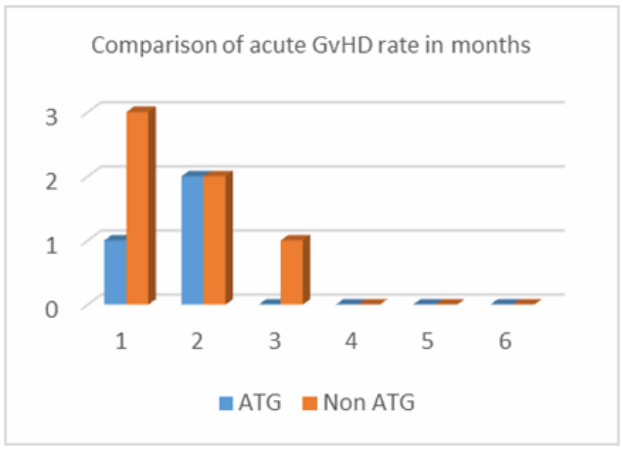

Fig. 10a.

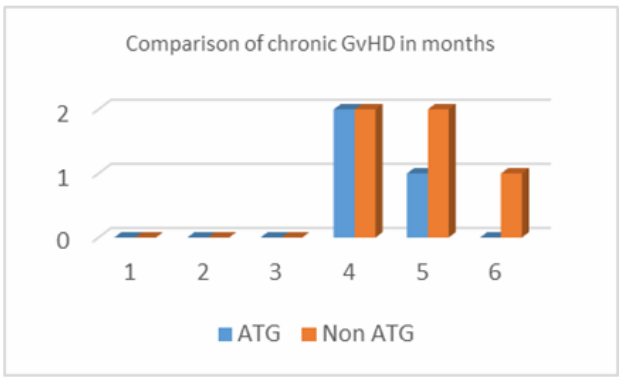

Fig. 10b.

Fig. 10. Comparison of acute GvHD between ATG and non ATG group

Figure 10 illustrates the comparison of acute and chronic GvHD rates in months after allogeneic HSCT.

The main „fear" of using ATG in conditioning of patients with AML is the reduction of the graft *versus* leukemia effect resulting in bigger relapse rates, and the increased rates of fatal infections.

In the ATG group, relapse was confirmed in 3 patients (15.7%), whereas in the non-ATG group in 4 patients (19%). Regarding infections, in the ATG group serious infections were diagnosed in 5 patients (26%), while in the non-ATG group in 3 patients (14%) (Figure 11).

If we compare the overall survival in these 2 groups of patients, we will see that in the ATG group, the OS is not inferior compared to the non-ATG group (Figure 12).

If we compare the relapse rate, we can see that there was no significant difference in these 2 groups of patients (Figure 13).

But, regarding the rates of GvHD in the ATG and non-ATG group, we found a significant difference in the rates of acute and chronic GvHD in favor of the ATG group, or to be more precise, the ATG group had lower rates of diagnosed GvHD (Figure 14).

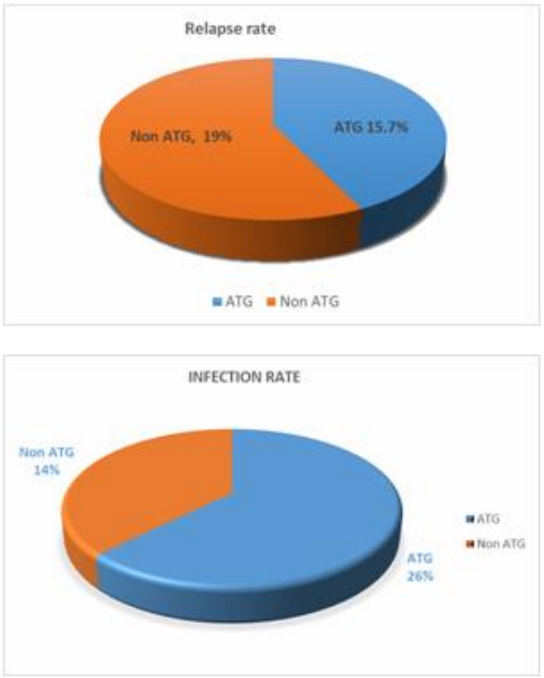

Fig. 11. Relapse rates and infection rates in ATG and non ATG patients

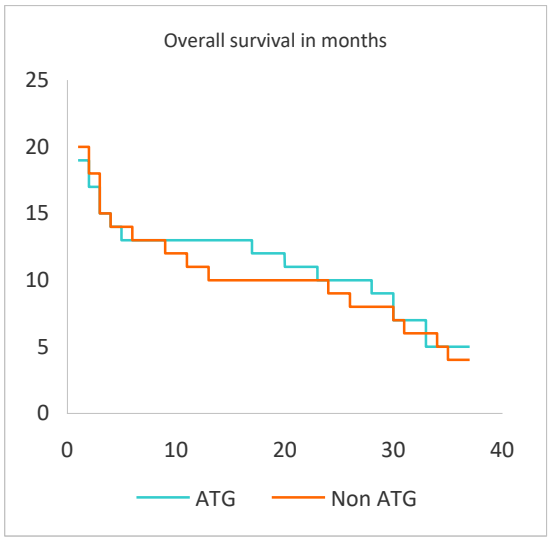

Fig. 12. Overall survival in ATG and non ATG group

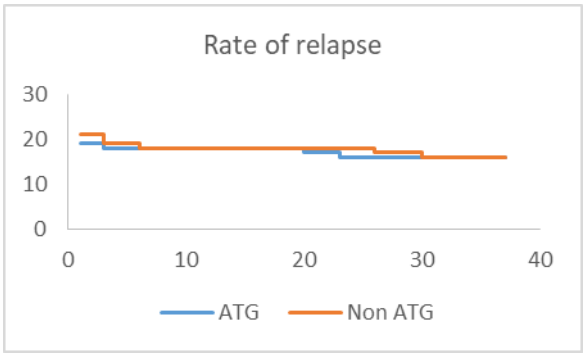

Fig. 13. Relapse rates in ATG and non ATG group

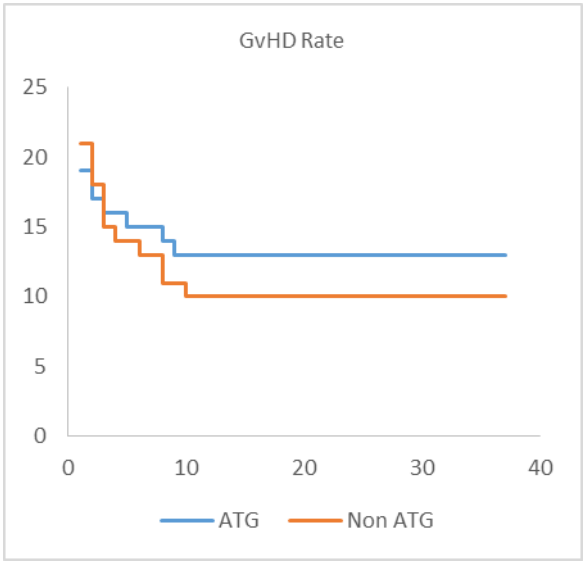

Fig. 14. GvHD rates in ATG and non ATG group

Discussion

Allogeneic HSCT is considered as a potentially curable therapeutic option for patients with AML. The main „weapon" against the malignant disease is the graft versus leukemia effect [15]; often hidden behind a GvHD manifesting after allogeneic HSCT. But GvHD represents a major complication after allogeneic HSCT worsening transplant-related mortality rates. Overall, 30-50% of patients will develop acute GvHD, and around 15% will have severe GvHD (grade III-IV). The main risk factor for developing chronic GvHD is previous acute GvHD. One of the possibilities to reduce the GvHD rates is to perform a T cell depletion *in vivo* by using ATG. This was the main reason to analyze our patients and the use of ATG in conditioning.

We used rabbit ATG, administered on days -3,-2,-1 at a dose of 5-10 mg/kg TT. We used a standard premedication. No serious adverse reactions were observed that would result in discontinuation of the drug, nor fatal adverse events resulting in patients' death. One of the main drawbacks for use of ATG is the increased relapse rates and increased infection rates that could lead to worse survival rates, increased mortality rates and low quality of life.

In order to see the pros and cons of the use of ATG we divided our analyzed group of patients in 2 groups, those receiving ATG in conditioning and those receiving conditioning without ATG. In almost all of our patients myeloablative conditioning was applied. In the posttransplant period, standard immunosuppression was managed with cyclosporine A + short course of methotrexate in most of the patients. The majority of patients where cytogenetics was available, were categorized in intermediate or poor risk groups.

In the ATG group, 15.8% were diagnosed with acute GvHD, and the same percentage accounted for the chronic GvHD. The non-ATG group had significantly higher rates of acute GvHD (29%) and chronic GvHD (24%). The worse grades of GvHD III-IV were detected in the non-ATG group *vs.* the ATG group (19% *vs.* 10%) and contributed more to the mortality rates of the patients.

Regarding the infection rates, it was higher in the ATG group than in the non-ATG group (26% *versus* 14%). But the majority of the infectious complications were treated successfully using rigorous microbiology testing and aggressive antibiotic therapy according to the antibiotic susceptibility findings. There was no difference in the rate of serious sepsis and TRM regarding infection complications. Slightly more CMV reactivation was noticed in the ATG group, but it was treated successfully. We did not detect fatal aspergillosis nor any other fungal infections. All our patients were on standard fungal prophylaxis with fluconazole 200 mg.

If we analyze the relapse rates, they were slightly bigger in the non-ATG group (19%) compared to the ATG group (15.7%). There were variables influencing these results mainly attributed to the worse risk profile of the disease in the non-ATG group of patients. There was no significant difference in the OS in both groups.

Conclusion

Using ATG in conditioning of patients with AML undergoing allogeneic HSCT as a method of *in vivo* T cell depletion represents a justified and save therapeutic method resulting in lower rates of GvHD, better quality of life, not worsening relapse rates and therapeutic potential of allogeneic HSCT.

Conflict of interest statement. None declared.

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ММР

Original article

PROGNOSTIC VALUE OF VON-WILLEBRAND FACTOR FOR PREDICTION OF CLINICAL EVENTS RELATED TO LIVER CIRRHOSIS AND PORTAL HYPERTENSION

ПРОГНОСТИЧКАТА ВРЕДНОСТ НА ВОН-ВИЛЕБРАНДОВИОТ ФАКТОР ЗА ПРЕДИКЦИЈА НА КЛИНИЧКИ НАСТАНИ ПОВРЗАНИ СО ЦРНОДРОБНА ЦИРОЗА И ПОРТНА ХИПЕРТЕНЗИЈА

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Abstract

Introduction. Von-Willebrand factor (vWF) has recently gained important prognostic value in patients with liver cirrhosis. The aim of the study was to analyze the relation between vWF and manifestations of portal hypertension and to evaluate the prognostic value of vWF for occurrence of clinical events and complications of liver cirrhosis and portal hypertension.
Methods. This prospective study comprised 71 patients with liver cirrhosis and portal hypertension. We initially evaluated the relation between vWF concentration and manifestations and complications of portal hypertension. We prospectively followed up patients for one year and we evaluated the predictive value of vWF for the occurrence of several clinical events and complications.
Results. The analysis showed no significant difference in the vWF concentration between the two groups of patients for any of the selected manifestations of portal hypertension. During the follow-up period, we registered 43 events in 29 out of 63 patients (46.03%). The worsening of the ascites was the most frequently encountered complication, registered in 10 (15.9%) patients. Regarding the prognostic value of vWF, the analysis did not confirm a significant predictive potential of vWF for occurrence of any of the selected clinical events.
Conclusion. The study showed that vWF was not a significant predictor of complications and clinical events related to liver cirrhosis and portal hypertension.

Keywords: von-Willebrand factor, liver cirrhosis, portal hypertension, clinical event, prediction, prognosis

Апстракт

Вовед. Фон-Вилебрандовиот фактор (фВФ) од неодамна се здоби со важна прогностичка вредност кај пациенти со црнодробна цироза. Цел на студијата беше да се анализира поврзаноста помеѓу фВФ и манифестациите на портна хипертензија и да се евалуира прогностичката вредност на vWF за предикција на клинички настани и компликации поврзани со црнодробната цироза и портната хипертензија.
Методи. Оваа проспективна студија опфати 71 пациент со црнодробна цироза и портна хипертензија. Првично ја евалуиравме поврзаноста помеѓу концентрацијата на фВФ и манифестациите и компликациите на портна хипертензија. Проспективно ги следевме пациентите во тек на една година и ја евалуиравме предиктивната вредност на фВФ за појава на неколку клинички настани и компликации.
Резултати. Анализата не покажа присуство на значајна разлика во концентрацијата на фВФ помеѓу двете групи пациенти за која било од избраните манифестации на портна хипертензија. Во текот на периодот на следење, регистриравме 43 настани кај 29 од 63 пациенти (46.03%). Појавата на влошување на асцитот беше најчестата компликација, регистрирана кај 10(15.9%) пациенти. Во однос на прогностичката вредност на фВФ, анализата не потврди значителен предиктивен потенцијал на фВФ за појава на кој било од селектираните клинички настани.
Заклучок. Студијата покажа дека vWF не е значаен предиктор за компликации и клинички настани поврзани со цироза на црниот дроб и портална хипертензија.

Клучни зборови: фон-Вилебрандов фактор, црнодробна цироза, портна хипертензија, клинички настан, предикција, прогноза

Introduction

Portal hypertension (PH) develops as a consequence of the structural abnormalities of the hepatic vascular architecture in cirrhotic patients and it is an entity that goes along with the natural course of advanced chronic liver disease. More importantly, PH underlies most of

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the related life-threatening complications that are associated with high morbidity and mortality in these patients [1]. The hepatic venous pressure gradient (HVPG) is the gold standard diagnostic tool for determining the presence and severity of PH [2,3]. However, some new, non-invasive biological variables have recently emerged as useful prognostic indicators of PH [4]. Von-Willebrand factor (vWF), an indicator of endothelial dysfunction [5-7] has recently gained some important prognostic value in cirrhotic patients [8-10]. Literature data suggest that in patients with liver cirrhosis vWF correlates with HVPG, CTP and MELD score [9], predicts clinically-significant PH, [4,8,9], and is a significant independent mortality predictor [9-11].

Since vWF corelates with HVPG and predicts clinically significant PH, we hypothesized that vWF could also predict the occurrence of clinical evets related to PH. Few studies have evaluated the association between vWF and some complications of PH [10,11], but the predictive value of vWF regarding the PH-related events has not been widely investigated.

The aim of the study was to analyze the relation between vWF and manifestations of PH and to evaluate the predictive value of vWF for occurrence of clinical events and complications of liver cirrhosis and PH.

Material and methods

This prospective study was performed at the University Clinic for Gastroenterohepatology in Skopje and it included 71 patients with liver cirrhosis and PH. We defined the presence of PH by the presence of indirect clinical and morphological signs and symptoms (physical examination, ultrasound image and gastroscopy findings). At enrolment we performed complete physical examination, abdominal ultrasound and gas analyses in capillary blood sample, biochemical analysis of blood, and we measured the vWF concentration. The vWF analysis was performed by using the immunoturbidimetric method on an automatic coagulometer (BCS XP System-Siemens Healthiness Global device) and the normal range of vWF was 50%-150%. Afterwards, we registered the presence of several findings indicating PH [the value of the alveolar to arterial oxygen gradient (A-a O_2), portal vein diameter on ultrasound, presence of ascites, oesophageal varices, enlarged spleen, encephalopathy, hepatorenal syndrome (HRS), hepatopulmonary syndrome (HPS) and mean arterial pressure (MAP)]. According to the presence of AD at presentation, we divided the patients in two groups. We prospectively followed up patients for one year and by following specific diagnostic criteria [12-16], during the follow-up period we registered the occurrence

Table 1. Analysis of vWF according to complications and manifestations of portal hypertension

Parameter	vWF							P
	N	$\overline{X}$ ± SD	Min	Max	Percentiles 25th	Median	75th	
A-a O_2 – alveolar arterial gradient								
≤15	9	284.0±132.3	167.0	586.0	195.0	225.0	337.0	Mann-Whitney U test:
>15	61	357.8±158.0	150.0	850.0	231.0	341.0	411.5	Z=1.5528; p=0.1205
Diameter of the portal vein (mm)								
≤13	11	334.8±130.0	167.0	586.0	239.0	342.0	400.0	Mann-Whitney U test: Z=-
>13	60	348.3±161.2	150.0	850.0	207.2	317.7	410.8	0.0079; p=0.9937
Ascites								
No	17	306.0±134.1	167.0	586.0	199.0	234.0	405.0	Mann-Whitney U test:
Yes	54	358.8±161.3	150.0	850.0	231.0	336.8	410.1	Z=1.2194; p=0.2227
Varices								
No	19	400.3±160.5	179.0	650.0	225.0	400.0	572.0	Mann-Whitney U test: Z=-
Yes	54	358.8±161.3	150.0	850.0	231.0	336.8	410.1	1.8314; p=0.0670
Enlarged spleen								
No	22	365.5±122.7	190.0	586.0	258.0	347.0	458.9	Mann-Whitney U test: Z=-
Yes	54	358.8±161.3	150.0	850.0	231.0	336.8	410.1	1.1502; p=0.2501
Encephalopathy								
No	51	340.2±157.8	150.0	850.0	216.0	307.0	410.1	Mann-Whitney U test: Z=-
Yes	54	358.8±161.3	150.0	850.0	231.0	336.8	410.1	0.6903; p=0.4900
Hepatorenal syndrome								
No	62	337.9±154.0	150.0	850.0	214.0	303.5	410.0	Mann-Whitney U test: Z=-
Yes	54	358.8±161.3	150.0	850.0	231.0	336.8	410.1	1.2271; p=0.2198
Hepatopulmonary syndrome								
No	9	284.0±132.3	167.0	586.0	195.0	225.0	337.0	Mann-Whitney U test:
Yes	54	358.8±161.3	150.0	850.0	231.0	336.8	410.1	Z=1.5528; p=0.1205
Mean arterial pressure (mmHg)								
≤70	5	269.0±114.2	161.0	400.6	198.0	200.3	385.0	Mann-Whitney U test:
>70	66	352.0±157.8	150.0	850.0	218.0	327.5	411.5	Z=1.2585; p=0.2082

*significant for p<0.05

of several clinical events representing acute decompensation (variceal bleeding, new-onset ascites, worsened ascites, infection, encephalopathy, HRSy and portal vein thrombosis).

We analyzed the quantitative series by using the measures of central tendency (average, median, minimum values, maximum values, interactive ranks) and dispersion measures (standard deviation, standard error). By using the Mann-Witney test we analyzed the difference in the vWF concentration between the two groups of patients (A-a $O_2 \leq 15$ vs. >15, diameter of the portal

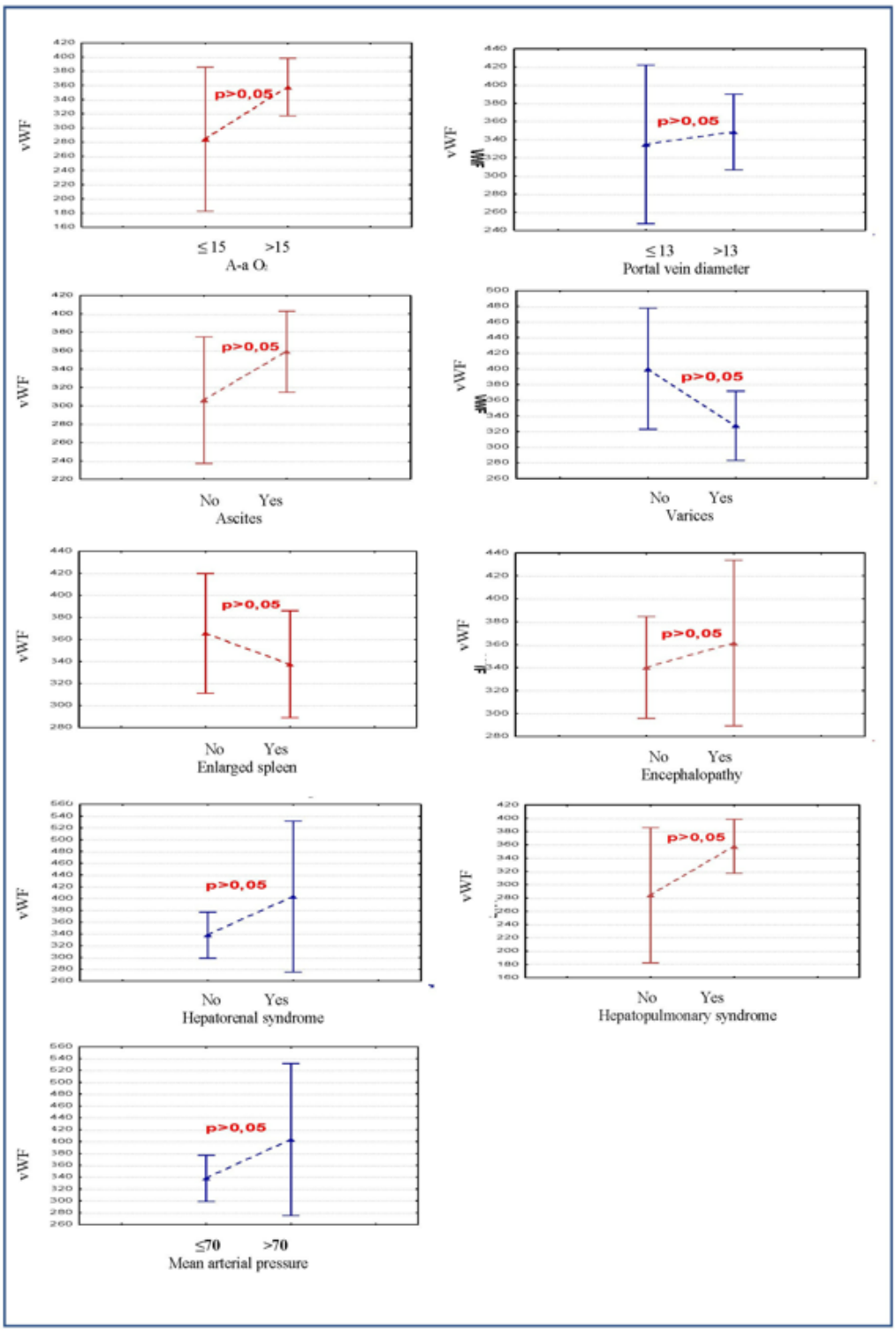

Fig. 1. Analysis of vWF according to the manifestations and complications of PH

vein ≤13 vs. >13, presence vs. absence of ascites, presence vs. absence of varices, presence vs. absence of enlarged spleen, presence vs. absence of encephalopathy, presence vs. absence of HRS, presence vs. Absence of HPS, MAP ≤ 70 vs. >70). In the prospective part that was performed on a sample of 63 patients, by using the univariate logistic regression analysis we evaluated the predictive value of vWF for the occurrence of the selected clinical events. A level of $p < 0.05$ was used to determine the statistical significance. All patients signed an informed consent for participation in the study. The study protocol was in line with the ethical principles of the Helsinki Declaration and it was approved by the Ethics Committee of the Faculty of Medicine at Ss. Cyril and Methodius University in Skopje.

Results

The analysis showed that elevated A-a O_2 was detected in 9 (12.9%), dilated portal vein above 13 mm in 60 (84.5%), ascites in 54 (76.1%), varices in 49 (72.1%), enlarged spleen in 49 (69.9%), encephalopathy in 20 (28.2%), HRS in 9 (12.7%), HPS in 61 (87.1%), and reduced MAP bellow 70 mm Hg in 5 (7%) patients. We analyzed the difference in the vWF concentration between the two groups of patients regarding each of the selected manifestations and complications of PH. The analysis showed no significant difference in the vWF concentration between the two groups of patients for any of the selected variables (Table 1, Figure 1).

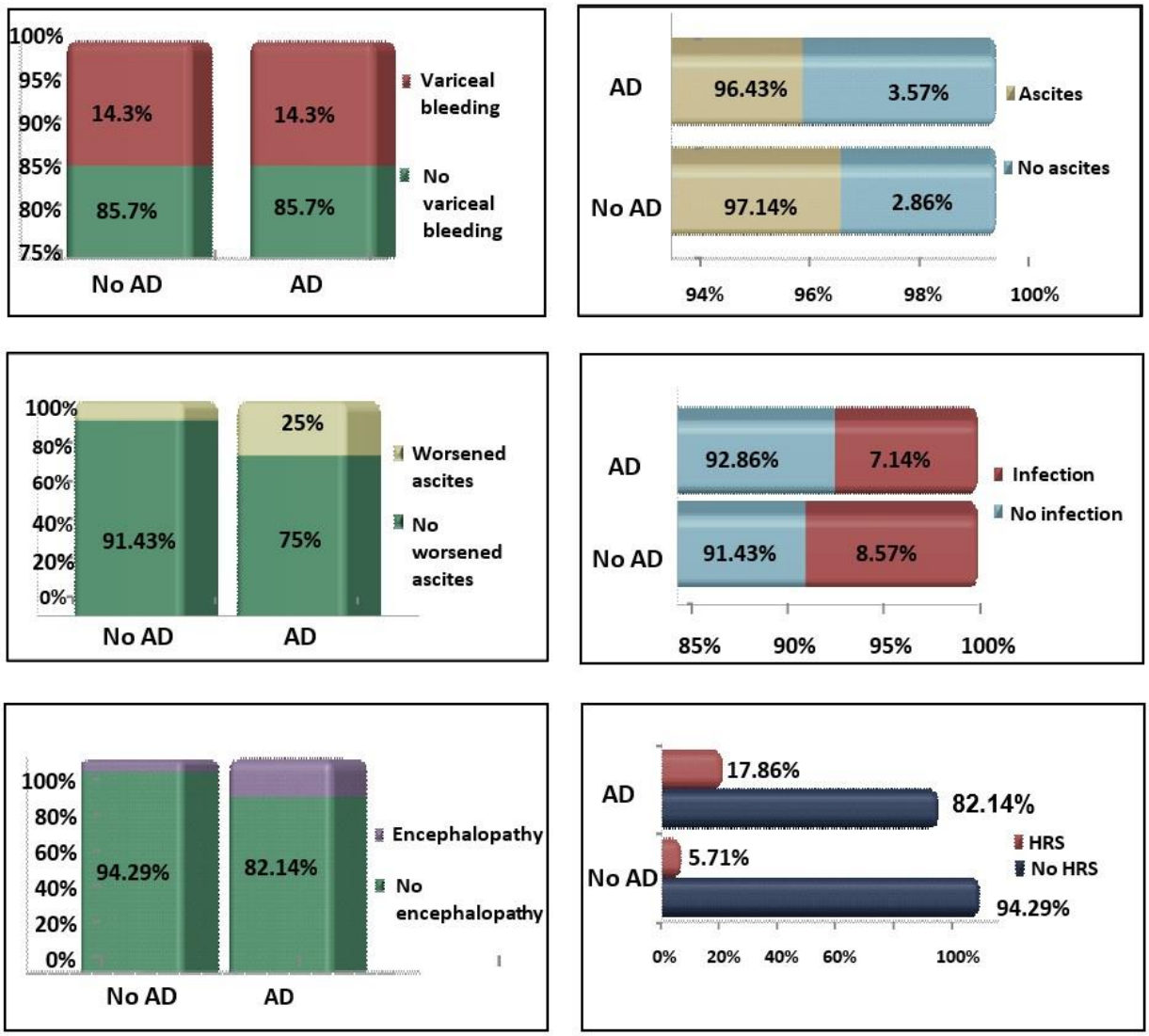

Fig. 2. Analysis acording to the initial AD status and the occurrence of clinical events related to liver cirrhosis and portal hypertension

During the follow-up period we registered occurrence of several events related to liver cirrhosis and PH [43 events in 29 out of 63 patients (46.03%)]. We Registered a new episode of variceal bleeding in 9 (14.3%), new-onset ascites in 2 (3.2%), worsened ascites in 10 (15.9%), infection in 5(7.9%), encephalopathy in 7(11.1%), HRSy in 7(11.1%) and portal vein thrombosis in 3 (4.8%) patients (Figure 2). We also analyzed the prog-

nostic role of vWF for prediction of these selected clinical events. The analysis (of the whole sample and of the two separate groups according to the initial AD status) confirmed that vWF was not a significant predictor for any of the selected clinical events ($p< 0.05$) (Table 2).

Table 2. Univariate logistic regression analysis of the predictive value of vWF for occurrence of selected clinical events

	AD status	B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
Vwf	No	(.024)	.014	2.828	1	.093	.977	.950	1.004
	Yes	(.001)	.003	.132	1	.716	.999	.993	1.005
	Total	(.003)	.003	1.223	1	.269	.997	.991	1.002
	Dependent variable – variceal bleeding no/yes						* significant for p<0.05		
vWF	No	(.059)	.060	.971	1	.325	.943	.839	1.060
	Yes	(.003)	.007	.248	1	.618	.997	.984	1.010
	Total	(.005)	.007	.560	1	.454	.995	.981	1.009
	Dependent variable – new-onset ascites no/yes						* significant for p<0.05		
vWF	No	.007	.006	1.316	1	.251	1.007	.995	1.019
	Yes	(.001)	.002	.088	1	.767	.999	.994	1.004
	Total	.002	.002	.956	1	.328	1.002	.998	1.006
	Dependent variable – worsened ascites no/yes						* significant for p<0.05		
vWF	No	(.010)	.010	.939	1	.333	.990	.971	1.010
	Yes	.003	.004	.594	1	.441	1.003	.995	1.011
	Total	.000	.003	.000	1	.987	1.000	.994	1.006
	Dependent variable – infection no/yes						significant for p<0.05		
vWF	No	(.001)	.008	.020	1	.889	.999	.983	1.015
	Yes	.000	.003	.013	1	.908	1.000	.995	1.006
	Total	.002	.002	.636	1	.425	1.002	.997	1.006
	Dependent variable – encephalopathy no/yes						* significant for p<0.05		
vWF	No	.012	.008	2.304	1	.129	1.013	.996	1.029
	Yes	.002	.003	.421	1	.516	1.002	.996	1.007
	Total	.004	.002	3.217	1	.073	1.004	1.000	1.009
	Dependent variable – HRS no/yes				* significant for p<0.05				
vWF	No	(.003)	.008	.207	1	.649	.997	.982	1.011
	Yes	/	/	/	/	/	/	/	/
	Total	(.006)	.006	.976	1	.323	.994	.982	1.006
	Dependent variable – portal vein thrombosis						* significant for p<0.05		

Discussion

The prognostic value of vWF in patients with liver cirrhosis a challenging scientific topic. PH is caused by the increased intrahepatic vascular resistance due to the intrahepatic vasoconstriction and by the increased systemic vasodilation leading to an increased portal flow. Being involved in both main mechanisms, the endothelial dysfunction plays a crucial role in the pathogenesis of PH. Since vWF is considered an indicator of ED, it has recently also raised remarkable interest as a useful prognostic indicator in cirrhotic patients [8,9-11]. Moreover, some research indicated that the increased vWF concentration is additionally involved in the progression of PH [17], a fact that makes vWF even more important prognostic indicator.

La Mura *et al.* evaluated the prognostic value of vWF in cirrhotic patients and proved that vWF was independently associated with survival free of PH-related events and of transplantation [9], but the prognostic value of vWF for prediction of complication of PH was not directly investigated. There are only few studies in the literature that evaluated the prognostic value of vWF for occurrence of clinical events in cirrhotic patents and most of them came across similar results. Ferlitsch *et al*. evaluated the prognostic value of vWF for prediction of PH, decompensation and mortality in cirrhotic patients. Despite the significant independent predicttive value for mortality, the study confirmed that vWF concentration correlated with the HVPG, predicted clinically significant PH and that higher vWF concentration was associated with the presence of varices (odds ratio [OR] 5 3.27; P<0.001) and ascites (OR 5 3.93; P<0.001) [10]. Kalambokis *et al*. also confirmed that vWF was an independent predictor for the occurrence of ascites and variceal bleeding [11], while Horvatits T *et al*. confirmed that vWF was an independent predictor of HPS [18]

Contrary to the results published in the previous research, our study did not confirm a significant difference in the vWF values between patients with/without manifestations of PH and vWF was not a significant predictor for any of the selected clinical events. The explanation behind these findings can be due to several reasons. The subjective component during evaluation of the presence of some events, the applied diagnostic criteria and cut-off values could play a certain role. Also, the small number of patients and clinical events in the study and the relatively short follow-up could significantly contribute to the study results.

In conclusion, our study did not confirm vWF to be a significant predictor of PH-related events. However, in patients with liver cirrhosis vWF is a biological variable with promising prognostic potential which prognostic value should be additionally evaluated in appropriately designed large prospective studies with longer follow-up.

Conflict of interest statement. None declared.

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ММР

Original article

HISTOPATHOLOGIC FINDINGS OF DIMINUTIVE AND SMALL COLORECTAL ADENOMA

ПАТОХИСТОЛОШКИ НАОДИ КАЈ МИНУТНИ И МАЛИ АДЕНОМАТОЗНИ КОЛОРЕКТАЛНИ ПОЛИПИ

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Abstract

Introduction. The largest number of polyps encountered during a colonoscopy are diminutive and small polyps less than 1 cm in size. Polypectomy is necessary to interrupt the adenoma-carcinoma sequence, and histopathology to discover advanced histological changes such as dysplasia or cancer. The estimation of dysplasia or carcinoma prevalence in diminutive and small polyps measuring 4-10 mm in diameter will help in using the "resect and discard" strategy during routine colonoscopy surveillance.

Methods. This prospective study comprised 201 patients in whom 344 colonic adenomatous polyps were detected ranging in size from 4 to 10 mm, which were removed during colonoscopy. Resected polyps were sent for pathologic assessment.

Results. A total of 201 patients were included in the study with resected 344 adenomatous polyps measuring 4-10 mm in size. Of these, 94.5% were adenomatous polyps without dysplasia, 4.6% had low-grade dysplasia, 0.3% villous polyp with low grade dysplasia, and 0.6% lost polyp. There were no polyps with high-grade dysplasia nor polyps with cancer. 54.7% of patients were males, and 45.3% females, $p<0.05$. In 40.1% of patients, indication for examination was bleeding.

35.8% of polyps were registered in sigma; the percentage difference between location in sigma *versus* other locations was significant, $p<0.05$.

Conclusions. Polyps measuring 4-10 mm in diameter had no advanced pathology such as high-grade dysplasia or carcinoma.

Keywords: colonoscopy; polypectomy; dysplasia; NBI

Апстракт

Вовед. Наголем број од полипите пронајдени во тек на колоноскопските прегледи се минутните полипи со големина под 1 цм. Полипектомијата е потребна да се прекине секвенцата аденома-карцином, а патохистолошката обработка за да се откријат напредната хистолошки промени како дисплазија или карцином. Процена на преваленцата на дисплазија или карцином во минутните и мали полипи со големина од 4-10 мм ќе овозможи да се користи "resect and discard" стратегијата при редовните колоноскопски прегледи.

Методи. Оваа проспективна студија опфаќа 201 пациенти кои имаат 344 откриени колонски аденоматозни полипи со големина од 4-10 мм кои се полипектомирани во тек на колоноскопскиот преглед. Ресецираните полипи се праќаат на хистопатолошка анализа.

Резултати. Во студијата учествуваат 201 пациент со откриени 344 аденоматозни полипи со големина од 4-10 мм. Од полипите 94,5% се аденоматозни полипи без дисплазија, 4,6% имаат дисплазија од лесен тип, 0,3% вилозен полип со дисплазија од лесен тип, 0,6% изгубен полип. Нема полипи со дисплазија од тежок тип ниту полип со карцином. 54.7% од пациентите се од машкиот пол, а 45.3% се од женски пол, $p<0.05$ (Difference test,p=.0444). Индикацијата за преглед кај 40.1% е крварење.

Во 35.8% од полипите се регистрирани на сигма, процентуалната разлика помеѓу локализација на сигма верзус останатите локализации е сигнификантна за $p<0.05$.

Заклучок. Полипите со големина од 4-10 мм немаат напредната патохистолошки наоди како дисплазија од тежок тип или карцином.

Клучни зборови: колоноскопија, полипектомија, дисплазија, NBI.

Introduction

According to GLOBOCAN 2020 estimates, there were 1.93 million new colorectal cancers (CRC) cases diagnosed in 2020 worldwide, representing 10% of all newly detected (19.3 million) cancers. Of these, 0.94 million death cases were a result of colorectal cancer

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in 2020 [1]. It is projected that the number of new colorectal cancer cases will reach 3.2 million by 2040 [2].
Colorectal cancer mainly arises from adenomatous polyps. Prevention of this type of cancer is possible by conducting a colonoscopy when polypectomy of colonic polyps is performed [3].
Endoscopic polypectomy is a resection of colonic polyps by which interruption of adenoma-carcinoma sequence is made [4].
In 1.7% or less than 1% of polyps up to 10 mm in size can have dysplasia [5,22]. According to other studies, presence of cancer cells can be found in ≤1% [6]. With the polyp growth, the chance of presence of malignant cells is increased [7]. Polyps larger than 10 mm have 10% higher chance of malignancy. More than 70% of large polyps have advanced pathology [22].
There is also a risk of high-grade dysplasia and carcinoma in small polyps. Polypectomy of polyps with advanced histopathological finding prevent development of colonic cancer. Since there is a small risk of development a high-grade dysplasia and even smaller risk of cancer, there is a possibility of "resect and discard" strategy for reducing the economic cost for histopathology of resected polyps and less time consuming of the very procedure [8,9]. However, there is a potential risk of removing a diminutive or small polyp that is malignant or with a high-grade dysplasia, but not send for histopathology and not controlling the site of resected carcinoma in a timely manner [10,11], which would further enable vascular and lymphatic invasion [12]. Particular attention to this procedure is required for polyps measuring 6-9 mm and right-sided colon polyps [13,22].
Nine percent of all colorectal carcinoma are developed after colonoscopy or polypectomy [14]. This can be a result of incomplete colonoscopy, i.e., the intubation of the colonoscope is not up to the cecum/terminal ileum, unregistered adenomas and malignant lesions, incomplete polyp resection, ''resect and discard'' strategy. Thus, it is important to choose an ideal method that enables complete resection without leaving any residual adenomatous tissue and assessment of the polyp with optical imaging for advanced histological changes such as cancer [15].
Narrow-band imaging (NBI) helps in discovering whether the polyp is neoplastic or non-neoplastic, the presence/absence of dysplasia, villous polyp or cancer [16], diagnosing of hyperplastic and inflammatory polyps that cannot be resected if non-neoplastic, but are dealt with the method "diagnose and leave behind" [17,5]. In the case of polyps with signs of advanced finding on NBI, neither "resect and discard" nor "diagnose and leave behind" strategy is being applied.
The frequency of post-polypectomy surveillance timing depends on the number of polyps found in a patient, their size and histopathological finding [18].
Patients after performed polypectomy and long-term surveillance have a decreased incidence of onset of colorectal carcinoma [19].
The aim of this study was to assess the rate of advanced histological finding in resected adenomatous polyps measuring 4-10 mm resected during colonoscopy. Secondary aims: their location and prevalence among sexes, and indication for examination.

Material and methods

This was a prospective-analytical study performed in one general hospital by one gastroenterologist in a period of two years, and comprised sessile adenomas 4-10 mm in size. Two methods of polypectomy were used, hot snare and cold snare, by random choice. A total of 201 patients were included, with 344 detected sessile adenomatous polyps measuring 4-10 mm. Histological analysis was done by one doctor-specialist in pathology.
Olympus Elvis 190 Exera CV III was used for colonoscopy and polypectomy.

Protocol for colonoscopy with polypectomy [20]:

1. Prior to examination, each patient signed a consent for conducting colonoscopy and an informed consent for participation in the study.
2. Patients had previous diet preparation and took Macrogol for bowel cleansing.
3. Those patients that underwent the procedure under anesthesia signed an anesthesia drug list.
4. A complete colonoscopy was done, which means the colon along to cecum and terminal ileum was examined.
5. Each detected polyp measuring 4-10 mm was assessed with NBI by using the NICE classification for selection of adenomatous, hyperplastic and malignant polyps.
6. The study included only adenomatous sessile polyps 4-10 mm in size by using one of the two methods for polypectomy, hot or cold snare.
7. Following polypectomy, the polyp was sent for histopathological analysis [21].
8. After 5-7 days, the histological finding was noted showing low-grade, high-grade dysplasia or carcinoma.

Parameters registered in the study:

- Indication for colonoscopy: present symptoms (pain, bleeding, diarrhea, obstipation), positive family history for CRC, screening, check-up after operated cancer;
- Location of the polyp in the colon (rectum, sigmoid colon, descending colon, transverse colon, ascending colon, cecum);

- Sex, age;
- Histological finding (adenoma, low- or high-grade dysplasia, carcinoma).

Inclusion criteria:

Patients at the age of 18-80 years of both sexes with present adenomatous sessile polyps measuring 4-10 mm incidentally detected during colonoscopy.

Exclusion criteria:

Hemoglobin <70 g/dL; Hyperplastic polyps; Pendulous polyps; Juvenile polyps; Colon polyposis; Polyps less than 4 mm in size; Polyps larger than 10 mm; Malignant disease; Unclean colon; Age under 18 years; Age over 80 years.

Results

During a period of two years, a total of 443 polyps 4-20 mm in size were removed, and for the purposes of this study 344 adenomatous sessile polyps 4-10 mm in size were resected.
Of the polyps measuring 4-20 mm, 78% were polyps 4-10 mm in size.
Of all 201 included patients, 54.7% were males and 45.3% females; the percentage difference was statistically significant, for $p<0.05$ (Difference test, $p=.0444$) (Table 1, Figure 1a). The mean age of the examined group of patients was 55.3±12.1 years, ranging from 27 to 79 years. The mean age of male patients was 53.7±12.6 years, ranging from 27 to 79 years, and of female patients 57.2±11.3 years, ranging

Table 1. Demographic characteristics of examined patients who were registered to have polyps 4-10 mm in size

		N	Mean	Minimum	Maximum	Std. Dev.
Age		**201**	**55.32836**	**27.0**	**79.0**	**12.13184**
Age	***Men***	**110**	**53.75455**	**27.0**	**79.0**	**12.60929**
	Women	**91**	**57.23077**	**31.0**	**76.0**	**11.30592**
				N		**%**
Sex	***Men***			**110**		**54.7**
	Women			**91**		**45.3**

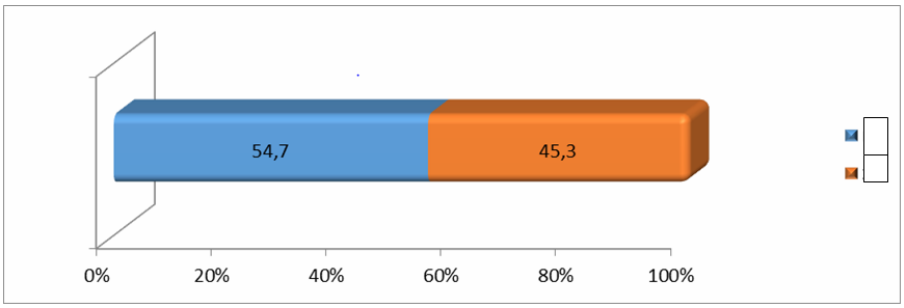

Fig. 1a. Patients distributed according to age who had polyps 4-10 mm in size

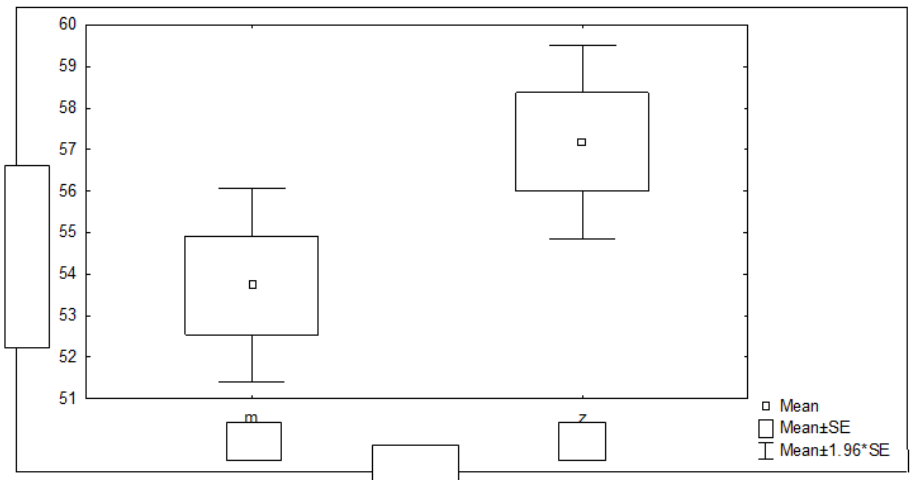

Fig. 1b. Mean age of patients distributed according to sex who had polyps 4-10 mm in size

Table 2. Indication, location and histopathological finding of detected polyps

Indications	N	%
pain	**46**	**22.8**
diarrhea	**17**	**8.4**
check-up after operated carcinoma	**15**	**7.4**
screening	**28**	**13.9**
obstipation	**8**	**4.0**
bleeding	**81**	**40.1**
anemia	**7**	**3.5**
Location		
rectum	**73**	**21.2**
sigma	**123**	**35.8**
colon descendens	**22**	**6.4**
flexura lienalis	**4**	**1.2**
colon transversum	**27**	**7.8**
flexura hepatica	**26**	**7.6**
colon ascendens	**53**	**15.4**
cecum	**14**	**4.1**
lost polyp	**2**	**0.6**
Finding		
adenoma	**325**	**94.5**
low-grade dysplasia	**16**	**4.6**
villous type with low-grade dysplasia	**1**	**0.3**
lost polyp	**2**	**0.6**

from 31 to 76 years (Table 1, Figure 1b). According to the t-test, the difference between the mean age with reference to sex was statistically significant, for $p<0.05$ (t-test=2.03453, p=043218).

In the largest percentage of patients (40.1%), the indication for examination was bleeding, in 22.8% it was pain, in 13.9% polyps were detected during screening, in 8.4% when diarrhea was registered, in 7.4% at the check-up after operated carcinoma, in 4% obstipation, in 3.5% anemia. The percentage difference between the indication bleeding *versus* the remaining modalities of indication was significant, for $p<0.05$ (Difference test, p=.0002) (Table 2).

According to the location, in the largest percentage of patients (35.8%), it was registered in the sigmoid colon, followed by 21.2% in rectum, 15.4% in ascending colon, 7.8% in transverse colon, 7,6% in right colic flexure, 6.4% in descending colon, 4.1% in cecum, and 1.2% in left colic flexure. The percentage difference between location in sigmoid colon *versus* the remaining locations was significant, for $p<0.05$ (Difference test, p=.0000) (Table 2).

A total of 342 polyps were sent to pathology. Two polyps were adenoma diagnosed only with narrow band imaging (Type 2-NICE classification), but were lost after polypectomy and they were not sent to pathology. 94.5% (325 polyps) of resected polyps were adenoma without advanced histopathological finding, 4.6% (16 polyps) were adenomas with low-grade dysplasia, 0.3% (1 polyp) was villous polyp with low-grade dysplasia. No polyps with high-grade dysplasia or cancer were found (Table 2).

Discussion

Polyps ranging 4 to 10 mm in size are of small risk for presence of high-grade dysplasia and cancer [22,23].

Subcentimeter polyps represent up to 97.6 % of polyps discovered during colonoscopy, and 0.3% of them less than 5 mm and 0.8% of polyps measuring 6-9 mm are with advanced histological changes [24].

According to another study, in a group of polyps measuring 6-9 mm a carcinoma was detected during histopathological analysis [25]. Therefore, colonoscopy with polypectomy is recommended for this size of polyps with pathological analysis [26].

Depending on the histological finding, colonoscopy surveillance is recommended.

In patients with one resected polyp ≥10 mm with a high-grade dysplasia or more than 5 adenomas, a control colonoscopy is recommended at three years, and in patients with 1-4 polyps <10 mm, with a low-grade dysplasia a control screening colonoscopy is recommended [27].

The "resect and discard" method can be used with particular caution and by using narrow-band imaging along with mandatory control colonoscopy surveillance.

Conflict of interest statement. None declared.

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Original article

THE CORRELATION BETWEEN HIGH BLOOD PRESSURE AND RISK OF ENDOMETRIAL MALIGNANCY IN POSTMENOPAUSAL WOMEN

КОРЕЛАЦИЈА ПОМЕЃУ ВИСОК КРВЕН ПРИТИСОК И ПОЈАВА НА ЕНДОМЕТРИЈАЛЕН МАЛИГНИТЕТ КАЈ ПОСТМЕНОПАУЗАЛНИ ПАЦИЕНТКИ

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Abstract

Introduction. Postmenopause is a period that starts one year after the last menstruation. Late menopause, after 70 years, is called senile.
Aim. To examine the correlation between high blood pressure and the risk of endometrial malignancy in postmenopause.
Methods. A prospective clinical study was conducted involving 120 postmenopausal patients treated at the University Clinic for Gynecology and Obstetrics in Skopje, divided into two groups: control and examined. The control group included 40 postmenopausal patients, hospitalized and operated due to urogenital pathology. The examined group consisted of 80 patients. A detailed history of patients was taken and blood pressure was measured, intervention was taken from both groups, and the material obtained was sent for histopathological analysis to determine eventual malignancy.
Results. In our study women with high blood pressure were 15.724 [p=0.010, 95% CI=1.932-27.952] times more likely to have endometrial cancer compared to women with normal blood pressure.
Conclusion. In postmenopausal patients, the likelyhood of endometrial cancer significantly increases with high blood pressure.

Keywords: postmenopause, high blood pressure, endometrial malignancy

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Абстракт

Вовед. Постменопаузата е период кој започнува една година по последната менструација. Доцната менопауза, по 70 години, се нарекува сениум.
Цел. Да се испита корелацијата помеѓу висок крвен притисок и ризикот од ендометријален малигнитет кај пациентките во постменопаузата.
Методи. Проспективна клиничка студија во која учествуваа 120 пациенти во постменопауза третирани на Универзитетската клиника за гинекологија и акушерство-Скопје, поделени во две групи: контролна и испитувана. Контролната група вклучуваше 40 пациенти во постменопауза, хоспитализирани и оперирани поради урогенитална патологија. Испитуваната група се состоеше од 80 пациенти. Беше земена детална анамнеза кај пациентките, мерен крвен притисок од двете групи ,и направена интервенција кај пациентите од двете групи, а материјалот беше испратен на хистопатолошка анализа за да се утврди присуство на евентуалниот малигнитет.
Резултати. Од испитувањето добивме дека пациентките со висок крвен притисок имаат 15,724 [p= 0,010, 95% CI=1,932-27,952] пати поголема веројатност да имаат рак на ендометриумот во споредба со жените со нормален крвен притисок.
Заклучок. Кај пациенти во постменопауза, веројатноста за појава на ендометријален карцином значително се зголемува со високиот притисок на крвта.

Клучни зборови: постменопауза, висок крвен притисок, ендометријален малигнитет.

Introduction

Menopause begins one year after the last menstrual cycle. In this period, a new source of oestrogens is estrone. It is divided into early and late menopause. Late menopause, after 70 years, is called senile. In 10-15% of cases, postmenopausal bleeding is caused by endometrial cancer, and usually abnormal uterine bleeding is caused by endometrial polyps or atrophy [1]. The incidence of endometrial cancer in postmenopausal patients is 0.7%, but it increases in patients with additional risk factors [2]. In this period, abnormal uterine bleeding belongs to polyps, endometrial atrophy, endometrial hyperplasia, endometrial carcinoma, submucosal fibroid, hormone therapy, uterine or uterine infections, use of certain drugs [3], etc.

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According to the International Federation of Gynecology and Oncology (FIGO), the stages are subclassified into two pathological types. Type 1-estrogen-dependent [4] in which in 30-80% of cases the mutation of the PTEN gene is responsible for this type of malignant tumor. It occurs from complex atypical hyperplasia [5], it is associated with estrogen stimulation and is not aggressive [6]. Type 2-neurostrogen-dependent endometrial cancer is poorly differentiated, with a deep myometrial invasion, including lymph nodes, low progestin sensitivity and 58% five-year survival [7,8]. It develops from an atrophic endometrium and is not associated with hormone stimulation [6]; it metastasizes and grows outside the uterine hull [6]. Mutations of the P53 gene occur in 50% of cases. Papillary serous carcinoma and mesonephron belong to this group. This neoplasia are very aggressive.

Aim

The aim of the study was to investigate the predictive role of the thickness of the endometrium in the onset of endometrial malignancy in postmenopausal patients.

Material and methods

This was a prospective clinical study including 120 postmenopausal patients treated at the University Clinic for Gynecology and Obstetrics in Skopje. Patients were divided into two groups: control and examined. The control group included 40 postmenopausal patients, hospitalized and operated due to urogenital pathology, with ultrasonically detected endometrial thickness less than 5 mm. The examined group included 80 postmenopausal patients hospitalized due to endometrial bleeding with an ultrasound detection of an endometrial thickness greater or equal to 5 mm. A detailed history of patients was taken and blood pressure was measured, intervention was taken from both groups, and the material obtained was sent for histopathological analysis to determine eventual malignancy.

The examined group excluded patients in generative reproductive age, patients who were not able to do fractional exploratory curettage, patients with a personal history of malignant disease (past or current), patients with a personal anemia for benign or malignant tumors of the ovary, breast cancer patients treated with tamoxifen, patients with any pelvic surgery due to other gynecological pathology.

Statistical analysis

Data were analyzed with the statistical package SPSS 20.0. The Pearson's Chi square test of homogeneity was used to establish an association between certain attributive dichotomies of the two groups of patients. The Shapiro-Wilk W test was used to determine the frequency distribution of certain variables. To test the signifycance of the difference between two and more numerical variables with regular or irregular distribution of frequencies Student's t-test for independent samples, Mann Whitney U test and Kruskal-Wallis ANOVA test were used. A level of $p < 0.05$ was considered to be statistically significant.

Results

According to Table 1, from the total number of respondents in the sample, hypertension control 65 (54.2%) of the respondents and that consequently in the examined and control group after 41 (51.2%) v.s. 24 (60%). There was no statistically significant difference in relation/absence of hypertension between the two groups, for $p>0.05$ (Pearson's Chi-square test: 0.8224, df=1, p=0.3645).

Table 1. Descriptive analysis of the sample by groups and hypertension

Hypertension		Group		Total amount
		Examined	Control	
Do not have	N	39	16	55
	%	48.75%	40%	45.83%
Have	N	41	24	65
	%	51.25%	60%	54.17%
Total amount	N	80	40	120
	%	66.67%	33.33%	100%

Pearson Chi-square=0.8224, df=1, p=0.3645, * significant for p<0.05

Table 2. Binary logistic regression analysis of the predictive role of certain parameters regarding endometrial malignancy - study group

Variable	B	S.E.	Wald	Df	Sig.	Exp(B)	% C.I. for EXP(B) Lower	Upper
High blood pressure – referent category/ high blood pressure not								
High blood pressure – yes	2.755	1.070	6.635	1	.010*	15.724	1.932	27.952

High blood pressure was a significant predictor of endometrial malignancy ($p<0.05$). Women with high blood pressure were 15.724 [p=0.010, 95% CI=1.932-27.952] times more likely to have endometrial cancer compared to women with normal blood pressure (Table 2).

Discussion

High blood pressure-is a significant predictor of endometrial malignancy ($p<0.05$). Women with high blood pressure were 15.724 [p=0.010, 95% CI=1.932-27.952] times more likely to have endometrial cancer compared to women with normal blood pressure.
Rothman *et al*. indicated a 5-fold increased risk of malignancy of the two risk factors, BMI and hypertension in their synergistic action [9].

Conflict of interest statement. None declared.

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ММР

Original article

THE CONNECTION BETWEEN ANTITHROMBIN 3, PLASMINOGEN ACTIVATOR INHIBITOR 1, VACUOLAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2, SOLUBLE TIE 2 IN MATERNAL PLASMA, WITH ABNORMAL PLACENTAL INVASION

ПОВРЗАНОСТА НА АНТИТРОМБИН 3, ПЛАЗМИНОГЕН АКТИВАТОР ИНХИБИТОР 1, ВАКУЛАРЕН ЕНДОТЕЛИЈАЛЕН ФАКТОР НА РАСТ РФЕЦЕПТОР 2, РАСТВОРИЛИВ ТИЕ 2 ВО МАЈЧИНА ПЛАЗМА, СО НЕПРАВИЛНАТА ПАЛЦЕНТАРНА ИНВАЗИЈА

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Abstract

Introduction. Abnormal placental invasion, placenta accreta spectrum (PAS), is an abnormally adherent placenta to the uterus with inability to detach properly after delivery of the fetus. Certain maternal plasma biomarkers show association with abnormal placental invasion.
Methods. This was a prospective cohort study, conducted at PHI UGAK, Skopje, Republic of North Macedonia from 02.2021 to 01. 2022. The study included 28 patients diagnosed with PAS. Maternal plasma samples were taken from all patients. The concentration of antithrombin III, plasminogen activator inhibitor 1 (PAI1), VEGFR2, Sol Tie 2 was measured in the third trimester of pregnancy.
Results. In all 28 patients, a diagnosis of PAS was detected, while previous ultrasound, placenta previa was diagnosed in 24 of these 28 patients, and the remaining 4 had ultrasound signs of placenta accreta. Meanwhile, the average value of antithrombin in the studied group was 192.1±28.2 my/ml, higher than in the control group which was 139.4±6.2 my/ml, with significance $p<0.05$ ($p=0.039853$). The average value of PAI in the studied group was 4.7±1.5 ng/ml, lower than in the control group which was 7.4±1.4 ng/ml, with significance $p<0.05$ ($p=0.000234$). The average value of VEGFR in the studied group was 7.1±1.7 ng/ml, higher than in the control group, which was 5.8±0.6 ng/ml, with signifycance $p<0.05$ ($p=0.039853$). The average value of Sol Tie in the studied group was 13.2±2.2 ng/ml, higher than in the control group, which was 10.8±0.9 ng/ml, with significance $p<0.05$ ($p=0.003532$). Regarding the values of the examined biomarkers, we can conclude that we obtained significant values.
Conclusion. The examination of these biomarkers can be used for prediction and early diagnosis of irregular pulsatile invasion. For this condition we validated the values as new biomarkers.

Keywords: antithrombin3, PAI1, VEGFR2, soluble TIE2, PAS

Апстракт

Вовед. Неправилна палцентарна инвазија, плацента акрета спектрум (ПАС**)** е абнормално атхерентна плацента за утерусот со неможност за правилно одлепување по породувањето на фетусот. Одредени биомаркери од мајчината плазма покажуваат поврзаност со неправилната плацентарна инавазија.
Методи. Оваа студија претставува проспективна кохортна студија, спроведена на ЈЗУ УГАК, Скопје, Република С. Македонија од 02.2021 год до 01. 2022 год. Во студијата беа вклучени 28 пациентки, со дијагноза на ПАС од кои се земаа примероци од мајчина плазма. Контролни случаи беа 10. Се изврши мерење на концентрација на **antithrombin III, plasminogen activator inhibitor 1(PAI1)**, **VEGFR2, Sol Tie 2** во третото тромесечје на бременоста.
Резулати. Кај сите 28 пациентки беше детектирана дијагноза на ПАС додека предходно ултразвучно, плацента превија беше дијагностицирана кај 24 од овие 28 пациентки, а останатите 4 имаа ултразвучни знаци за плацента акрета. Во однос на вредностите на биомаркерите, може да заклучиме дека кај сите биомаркери кои ги испитувавме добивме сигнификантно значајни вредости кои се за одбележување.
Заклучок. Испитувањето на овие биомаркери може да се употреби за предвидувње и рано дијагностицирање на неправилна палцентарна инвазија. Ги потврдивме вредностите како нови биомаркери за оваа состојба.

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Клучни зборови: Антитромбин3, ПАИ1, ВЕГФР2, растворлив Тие2, ПАС

Introduction

The placenta represents a primary support organ in the development of the fetus. The fertilized egg cell from the fallopian tube in the form of a morula reaches the uterine cavity and rapidly evolves into a blastocyst, and as such is implanted in the endometrium (5-6 days after fertilization). The outer layer of the blastocyst, from which the placenta later develops, transforms into a trophoblastic mass. From this trophoblastic mass follows the formation of trophoblastic villi and spaces, whereupon the first transfer of nutrients and gases between mother and fetus begins [1]. Before the 12th g.w the flow of plasma in the intervillous spaces is responsible for the exchange of substances and gases. After the 12th g.w, spiral arterioles are released from the trophoblast plugs, as flaccid and dilated blood vessels with low pressure, as a kind of reservoir of oxygen and nutrients for the fetus. That is the true uteroplacental circulation. A normal placenta at term (40 g.w.) has a diameter of 15-20 mm and a volume of 400-600 ml. Each gestational week the placenta grows approximately 1 mm in thickness; at term it should be 40-45 mm.

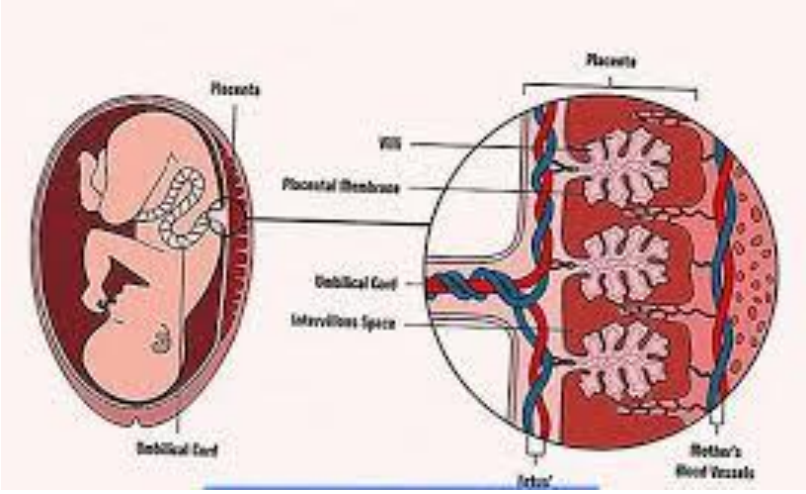

Fig 1. Placenta

Placenta accreta spectrum (PAS) represents an abnormal adherent placenta to the bearing of the uterine wall and the impossibility of its spontaneous detachment after delivery of the fetus or during cesarean section. It actually represents an irregular trophoblastic invasion of the trophoblast into the decidual changed endometrium. Placental trophoblastic cells have tissue invasive characteristics very similar to malignant neoplastic cells. When trophoblastic villi extend into a region with poorly developed or absent decidua, placenta accreta develops. The type of accreta varies depending on the depth of trophoblastic villi invasion (Figure 2). By definition, they are divided into: accreta - trophoblastic villi penetrate the entire thickness of the decidua, increta - trophoblastic villi penetrate and invade the myometrium but not the serosa and percreta - the trophoblastic villi penetrate through the myometrium into the serosa and also into the surrounding organs.

Placenta previa is a placenta that in the third trimester reaches the internal cervical opening and covers it partially or completely. When we talk about placenta previa, it should be noted that there are several subtypes of placenta previa (2) as follows:

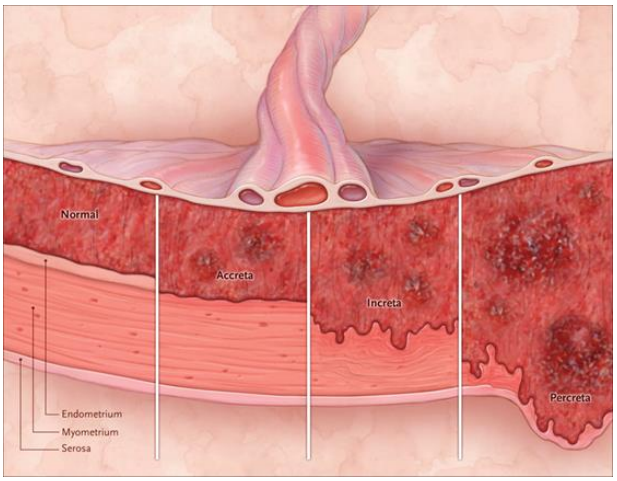

Fig. 2. PAS

- Low implanted placenta, which is located 2 cm from the internal uterine orifice (UU);
- Marginal placenta previa, which reaches the inner uterine orifice and does not cover it;
- Partial placenta previa, which partially but not completely covers the OUI;
- Total placenta previa, which completely covers the OUI

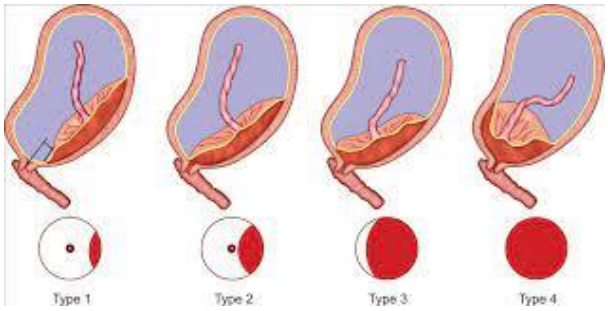

Fig. 3. Types of placenta previa

Ultrasound signs of PAS / Placenta previa: 1. "Clear zone" placenta bed, 2. Abnormal placental lacunae with turbulent flow, 3. Penetration into the bladder (the hyperechoic zone between the bladder and uterus is missing), 4. Placental protrusion towards the serosa, 5. Focal placental masses outside the uterus, 6. Placenta previa (total, partial, marginal)
Risk factors for placenta accreta spectrum are: *Regions of the uterus with poorly developed decidua (cervix), previous caesarean section, previous endometrial interventions, myomectomies, hysterotomies (scars), multiparous (multiple dilated uterus).*
In several studies, a significant increase of examined biomarkers, angiogenic, in maternal plasma was determined in conditions of PAS. In patients with signs of placenta accreta and/or placenta previa, due to the invasion of the uterine wall, certain angiogenic biomarkers enter the maternal circulation and at the same time show changed values. This highly regulated process depends on the complex crosstalk between the decidua and the endothelial and smooth muscle cells of the maternal blood vessels and thus invasive placental trophoblast invasion. The development of PAS occurs as a disorder of this process, leading to the inappropriate invasion of trophoblasts outside the decidua myometrium or outside of it.
Several biomarkers from mother's plasma, in the third trimester of pregnancy, were examined in various studies and were proven to be a quite significant field of interest due to the obtained values.

These include:
Antithrombin 3 - glycoprotein, part of the anticoagulant and inflammatory cascade, which blocks the formation of abnormal thrombi. It represents a balance between bleeding and coagulation.
Plasminogen activator inhibitor 1 (PAI) - has a function in preventing improper trophoblast invasion. Its downregulation, as in cases of PAS, may weaken the angiogenesis, reflecting a compensatory change.
Vascular endothelial growth factor receptor 2 - primary regulator of angiogenesis, as well as in the development of new blood vessels from the existing ones. It has a significant function in implantation, the formation of decidua and the maintenance of pregnancy.
Soluble Tie 2- is a receptor for Angiopoietin 1. It has a significant vascular function, as well as a role in the formation of the placenta [2,3].
The ground for this research was the increasing number of cesarean sections in the world as well as in our country, resulting in risk of PAS and related complications due to massive hemorrhages that occur after childbirth or cesarean section. Furthermore, the low sensitivity and specificity of ultrasound and MRI, which until now have been the only tools for the diagnosis of PAS.

Aim

The primary goal of this study was the antenatal determination of changed values of certain plasma biomarkers, as a prediction for PAS in patients from the risk group. The secondary goal was adequate care and hospitalization of these patients in a tertiary healthcare institution and delivery with prior preparation of professional teams and resources.

Materials and methods

This was a prospective cohort study that included 28 patients with a singleton pregnancy, a diagnosis of one or more previous caesareans and/or suspected PAS, placenta previa, aged 18-40 years in the third trimester of pregnancy. The control group consisted of 10 patients with a first, singleton pregnancy without comorbidities and with ultrasound signs of orderly placentation.
The study was conducted over a period of 3 months at the PHI University Clinic for Gynecology and Obstetrics, Skopje and the Institute of Immunology and Human Genetics, Skopje, in the period from January 1st to March 31st 2021. The examined group included female patients, outpatients or hospitalized at UGAK with Dg. St post SC, Re-SC, Tri-SC, PAS in the third trimester of pregnancy, in the Pathological and high-risk pregnancy department and the Peripartum intensive care department with previously determined ultrasound signs for PAS. When entering this study, all patients previously signed an informed consent to participate in the study, which was approved by the Ethics Committee at the Faculty of Medicine in Skopje, Republic of North Macedonia.
At the very beginning, a detailed general anamnesis was taken from the patients, followed by an exhaustive obstetric anamnesis about the number of previous pregnancies, the way they ended, the number of abortions, interventions or operations on the uterus.
Then, an ultrasound examination was performed, with an abdominal convex 3.5 MNz probe on a GE-Voluson 730 pro device in the outpatient clinic where they were examined or in the appropriate department where they were hospitalized. Ultrasound examination included fetal presentation, fetal biometry, heart rate, amount of amniotic fluid, determination of position, morphology,

maturity and invasion of the placenta into the uterine wall, according to the FIGO criteria for PAS.
According to the International Federation of Gynecology and Obstetrics (FIGO), abnormal placental invasion or PAS is divided by clinical and histological criteria into three sections [4,5].

1st degree - Adherent placenta (accreta)

*Clinical criteria - after vaginal delivery, the placenta does not separate after prescribing synthetic oxytocin and gentle traction of the umbilical cord. After manual revision of the uterine cavity, severe hemorrhage occurs and mechanical or surgical intervention is needed
- during caesarean section, there are no visible changes on the surface, only focal foci of bleeding
*Histological criteria - absent decidua in certain areas, i.e., the placental villi directly touch the myometrium.

2nd degree - Abnormally invasive placenta (increta)

*Clinical criteria - during a caesarean section, a bluish placental protrusion of the uterus is observed; hypervascularization with tortuous blood vessels on the surface; with gentle traction on the umbilical cord, that part of the uterine wall itself becomes indented.
*Histological criteria - placental villi at the level of the muscle fibers sometimes penetrate to the radial and arcuate blood vessels of the myometrium.

3rd degree - Abnormally invasive placenta (percreta)

3a-breakthrough of the serosa
*Clinical criteria - breakthrough of the placental tissue to the serosa, but not to the surrounding organs
*Histological criteria - the appearance of villous tissue through the serosa or literally 'cutting' of the uterine wall
3b-bladder perforation
*Clinical criteria - breakthrough of the placental tissue to the bladder without a clear border between it and the uterus
*Histological criteria - the villous tissue makes a 'cut' on the uterine wall and penetrates to the urothelium
3c-perforation of surrounding organs with or without the bladder
*Clinical criteria - breakthrough of the placental tissue to the broad ligament, vaginal fornices and any other pelvic organ
*Histological criteria - appearance of villous tissue in surrounding organs.
Two tubes of blood were taken, one with 2 ml of venous blood for differential blood count at UGAK and another 2 ml of venous blood for testing plasma biomarkers at the Institute of Immunobiology and Human Genetics. At the Institute of Immunology and Human Genetics, the blood was scalded at -20 degrees Celsius until it was used. Furthermore, the concentration of antithrombin III, plasminogen activator inhibitor 1, soluble Tie2, soluble vascular endothelial growth factor receptor 2 was measured using the ELISA method, the Luminex 200™ device. The test value was measured according to the manufacturer's reference values.
Inclusion criteria: singleton pregnancy, Uz and/or MRI signs of PAS, third trimester of pregnancy (28-37 g.w.), age 18-40 years.
Exclusion criteria: multiple pregnancy, hypertension, preeclampsia and diabetes.

Statistical processing

Data obtained were was processed with the statistical program SPSS for Windows 23.0. Numeric, i.e., quantitative parameters were shown with average, standard deviation. Qualitative, i.e., attributive parameters were shown by frequency distribution. The Mann-Whitney test was used to compare plasma biomarker concentrations. A value of $p<0.05$ was considered as statistically significant.

Results

The average value of antithrombin in the studied group was 192.1±28.2 my/ml, ranging from 146.6 to 265.6 my/ml and it was higher than the average value in the control group, which was 139.4±6.2 my/ml, ranging from 131.3 to 149.6 my/ml. ml (Table 1 and Figure 1a). The difference according to the Mann-Whitney U test was significant for $p<0.05$ ($p=0.000005$) (Table 2).

Table 1. Presentation of the average values of the studied parameters in the studied and control groups

Studied group	N	Average	Minimum	Maximum	Std.dev.
Antithrombin (my/ml)	28	192.1	146.6	265.6	28.24869
PAI (ng/ml)	28	4.7	2.7	7.9	1.54170
VEGFR (ng/ml)	28	7.1	4.1	9.7	1.67900
Sol Tie (ng/ml)	28	13.2	9.4	16.8	2.18076
Control group					
Antithrombin (my/ml)	10	139.4	131.3	149.6	6.245719
PAI (ng/ml)	10	7.4	5.9	9.9	1.392839
VEGFR (ng/ml)	10	5.8	5.1	6.7	0.594512
Sol Tie (ng/ml)	10	10.8	9.5	12.5	0.883428

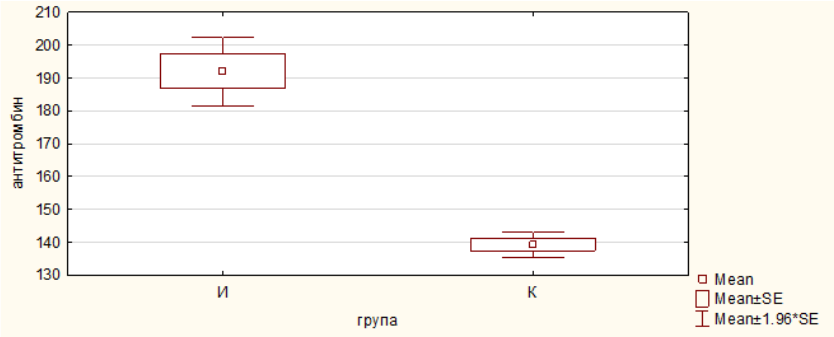

Fig. 1a. Presentation of the average values of antithrombin (my/ml) in the studied and control groups

The average value of PAI in the studied group was 4.7±1.5 ng/ml, ranging from 2.7 to 7.9 ng/ml and it was lower than the average value in the control group, which was 7.4± 1.4 ng/ml, ranging from 5.9 to 9.9 ng/ml. ml (Table 1 and Figure 1b). The difference according to the Mann-Whitney U test was significant for p<0.05 (p=0.000234) (Table 2).

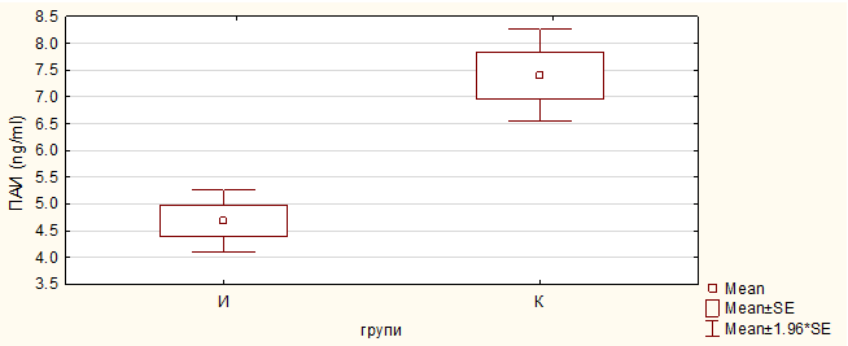

Fig. 1b. Presentation of the average values of PAI (ng/ml) in the studied and control groups

Table 2. Mann-Whitney U test results

Parameters	U	Z	p-value	No/IG	No/KG
Antithrombin (my/ml)	2.00000	4.55808	0.000005	28	10
PAI (ng/ml)	28.50000	-3.67961	0.000234	28	10
VEGFR (ng/ml)	77.50000	2.05528	0.039853	28	10
Sol Tie (ng/ml)	51.50000	2.91717	0.003532	28	10

The average value of VEGFR in the studied group was 7.1±1.7 ng/ml, ranging from 4.1 to 9.7 ng/ml and it was higher than the average value in the control group, which was 5.8±0.6 ng/ml, ranging from 5.1 to 6.7 ng/ml. ml (Table 1 and Figure 1c) The difference according to the Mann-Whitney U test was significant for p<0.05 (p=0.039853) (Table 2).

The average value of Sol Ti in the studied group was 13.2±2.2 ng/ml, ranging from 9.4 to 16.8 ng/ml and it was higher than the average value in the control group, which was 10.8±0.9 ng/ml, ranging from 9.5 to 12.5 ng/ml (Table 1 and Figure 1d). The difference according to the Mann-Whitney U test was significant for p<0.05 (p=0.003532) (Table 2).

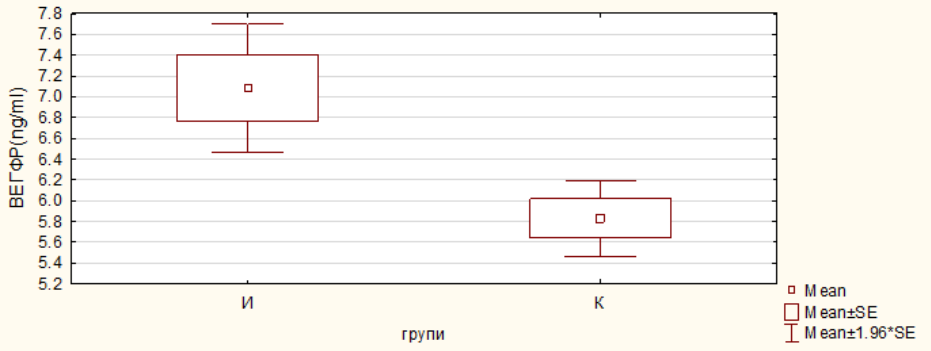

Fig. 1c. The average values of VEGF (ng/ml) in the studied and control groups

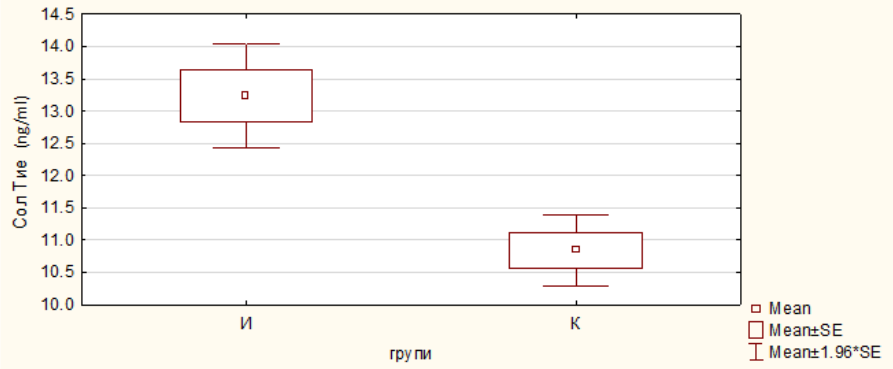

Fig. 1d. The average values of Sol Tie (ng/ml) in the studied and control groups

Discussion

The identification of a specific immune mediator and its concentration in the blood or plasma of a pregnant women has attracted a lot of attention as a potential source for diagnosis and therapy of this problem. This field remains underexplored because there are many differences in the research of various studies. The composition of maternal plasma changes during pregnancy, which has been proven in numerous studies [6].

Accordingly, plasma in a pregnant woman changes its composition during pregnancy and is influenced by various factors, such as: gestational week, uterine perfusion, various pathologies in pregnancy and many others. Especially in the second half of the pregnancy, the plasma composition seems to change significantly. Factors affecting the value of biomarkers have been researched in the past and numerous variables have been described, such as: ethnicity, fetal diseases, small for gestational age and body mass index [7].

The occurrence of PAS is increasing. Even with the best prenatal care, a significant percentage of cases are missed or diagnosed late, resulting in a significant maternal morbidity [8]. Hence, a new and improved diagnostic paradigm that uses biomarkers with ultrasound and other clinical tools is necessary and very important method.

In this study, we have provided initial evidence that is very significant for the continuation and development of a doctoral thesis, that several biomarkers present in maternal plasma are significantly elevated and can be used for early diagnosis of PAS [9]. Even with a limited sample size, - small number of patients? as in this study, the diagnostic performance of the 4 ELISA-validated biomarkers was sufficient to lead us to the conclusion that they can be used as part of a diagnostic panel.

Many of these protein markers may also contribute to further discovery of disease pathogenesis. For example, it is possible that the endothelium of these cellular proteins that are up-regulated in PAS are increased due to the increased vascular bed presented under conditions of placental invasion; with a significantly larger volume of endothelial cells, we expect a higher detectable level of their proteins [10]. However, some of these proteins, such as sTie2, may contribute to the abnormal placentation of vascular lakes observed in this condition, as the vascular phenotype is similar to those described in patients with genetic mutations in the Tie2 pathway [11].

Conclusion

If we summarize, we can conclude that the examination of these biomarkers is useful for prediction and early diagnosis of the disorder. We confirmed antithrombin III, PAI-1, soluble Tie2 and soluble receptor VEGF 2 as new biomarkers for this condition, compared to their values in the control group. We obtained significant values for all of them, but further studies are still needed to assess and confirm the significance, diagnosis and prognosis of PAS.

Conflict of interest statement. None declared.

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ММР

Case report

NEGLECTED CONDITION: NODULAR FASCIITIS AND OUR CASE

ЗАНЕМАРЕНА СОСТОЈБА: НОДУЛАРЕН ФАСЦИИТ И ПРИКАЗ НА НАШ СЛУЧАЈ

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Abstract

In 1955, nodular fasciitis was identified for the first time. Other names are infiltrative fasciitis, pseudosarcomatous fasciitis, and pseudosarcomatous fibromatosis. A quickly expanding lesion is the most typical sign of nodular fasciitis, and roughly half of the cases are accompanied by discomfort or pain. Depending on where the lesion is located, there are three basic types of nodular fasciitis: subcutaneous, intramuscular or fascial with intradermal and intravascular as unusual subtypes. We present an unusual case of a 52-year-old male with a 10+ year history of a tumor in the right gluteal region associated with pain during sitting in the last few months. The tumor may be grossly fibrous, myxoid, or even cystic and histopathologically, the tumor can be hypercellular and may imitate a sarcoma. Ultrasound can be helpful, but MRI is more accurate. However, the various histologic features make this tumor diagnostically nonspecific even on MRI with several differential diagnoses including fibrosarcoma, neurofibroma, and small fibrous histiocytoma. Fine-needle aspiration and histologic features may correlate well, but biopsy is typically necessary for a conclusive diagnosis.

Keywords: fasciitis, pseudosarcomatous fasciitis, surgical treatment

Апстракт

Во 1955 година, за прв пат беше идентификувана состојбата нодуларен фасцитис. Други имиња за оваа состојба се инфилтративен фасциитис, псевдосаркоматозна фасциитис и псевдосаркоматозна фиброматоза. Лезија која брзо се шири е најтипичен знак за нодуларен фасциитис, а приближно половина од случаевите се придружени со непријатност или болка. Во зависност од тоа каде се наоѓа лезијата, постојат три основни типови на нодуларен фасциитис: поткожен, интрамускулен или фасцијален со интрадермален и интраваскуларен како невообичаени подтипови. Прикажуваме необичен случај на 52-годишен маж со 10+ годишна историја на тумор во десната глутеална регија поврзана со болка при седење во последните неколку месеци. Туморот може да биде фиброзен, миксоид па дури и цистичен а хистопатолошки може да биде хиперцелуларен при што може да имитира сарком. Ултразвукот може да биде корисен, но магнетна резонанца е попрецизен. Сепак различните хистолошки карактеристики го прават овој тумор дијагностички неспецифичен дури и на магнетна резонанца со неколку диференцијални дијагнози вклучувајќи ги и фибросарком, неурофибром и малиген фиброзен хистиоцитом. Тенкоиглената аспирациона биопсија и хистолошките карактеристики може добро да корелираат, но ексцизионата биопсијата обично е неопходна за конечна дијагноза.

Клучни зборови: нодуларен фасциит, псеудосаркоматозен тумор, хируршки третман

Introduction

In 1955, nodular fasciitis was identified for the first time. Other names are infiltrative fasciitis, pseudosarcomatous fasciitis, and pseudosarcomatous fibromatosis [1]. It comprises benign, self-contained fibroblast growth with an unknown cause, not related to age, race or gender. Most of the patients are under the age of 50 (85%), while only 5% are over the age of 70 [2], located mostly at the upper extremities (48%) and torso (20%). Lower extremity (15%), neck and face (17%) are additional sites [3,4], while retroperitoneum [5], hand and foot [6] are examples of uncommon locations. It typically occurs as solitary lesion. Lesions can range

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in size between 5 to 100 mm, but 71% are 20 mm or smaller, with the majority being under 40 mm [2]. A quickly expanding lesion is the most typical sign of nodular fasciitis, and roughly half of the cases are accompanied by discomfort or pain [1]. Less common, numbness, paresthesia, and shooting pain indicate peripheral nerve compression [7].
Depending on where the lesion is located, there are three basic types of nodular fasciitis: subcutaneous, intramuscular or fascial with intradermal and intravascular as unusual subtypes [8].

Case report

We present an unusual case of a 52-year-old male with a 10+ year history of a tumor in the right gluteal region associated with pain during sitting in the last few months. Based on clinical examination and history, the tumor was diagnosed as sebaceous cyst. On physical examination, a 50 x 60 mm firm, subcutaneous, soft tissue tumor with pink to brownish discoloration of the perilesional skin was noted (Figure 1).

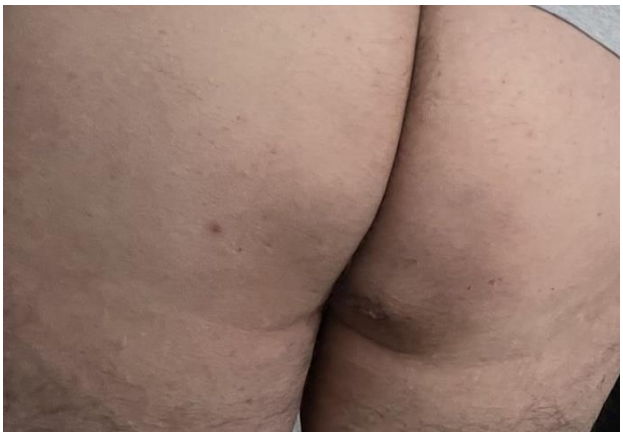

Fig. 1. Tumor in the right gluteal region

Lesion was attached to the underlying tissue that was seen during the examination. Due to its superficial localization, MRI, ultrasound or aspiration biopsy were not performed and the patient was admitted for one-day surgery. Longitudinal excision was done and the tumor was completely removed; the wound was closed and the sample was sent for histopathological analysis, as it was seen that macroscopically it did not look like a sebaceous cyst.
Histopathological examination revealed well-circumscribed tumor node in the subcutaneous tissue, composed of spindle cells with storiform pattern, minor nuclear pleomorphism, and foci of myxoid change and collagen deposition in the extracellular matrix (Figure 2).

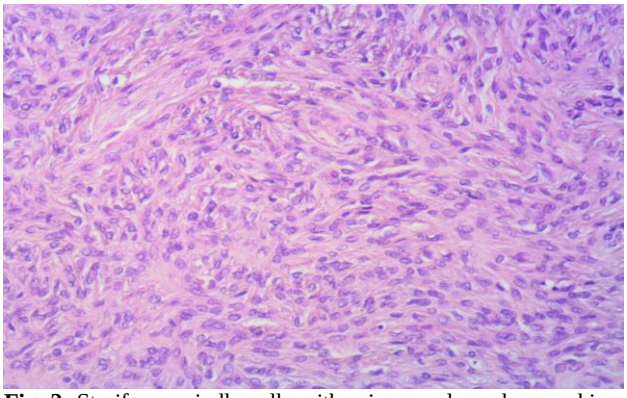

Fig. 2. Storiform spindle cells with minor nuclear pleomorphism and collagenous extracellular matrix (HeEo, x100)

Immunohistochemical analyses showed a focal positivity for smooth muscle actin (Figure 3), and negative staining for CD34 (Figure 4), S-100, Desmin and Caldesmon. The proliferative index on the staining with Ki67 was low, mainly <5%, with foci of up to 15% (Figure 5).

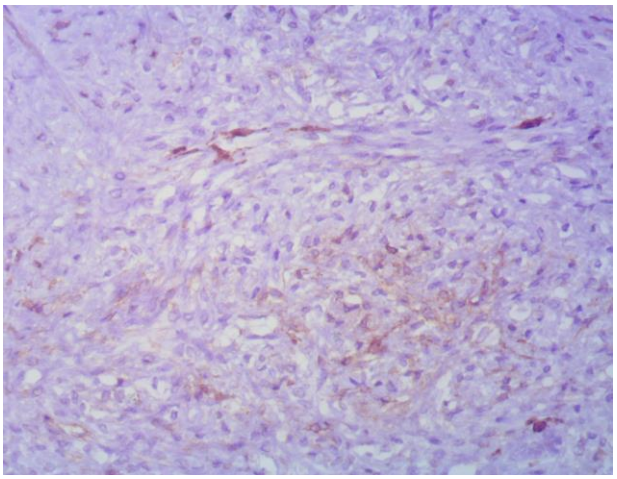

Fig. 3. Focal positivity for SMA, x100

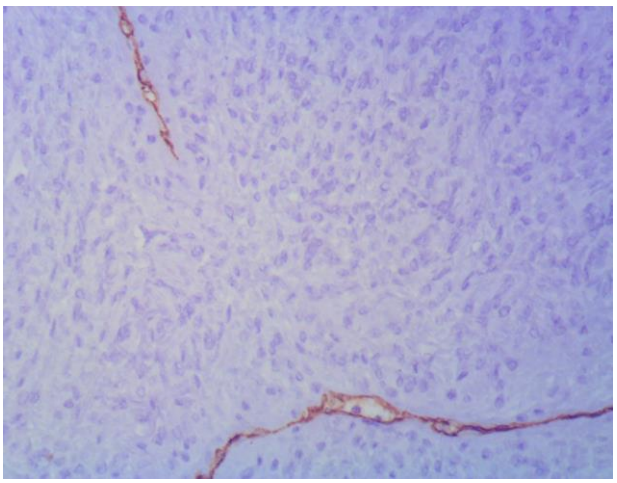

Fig. 4. CD34 negative tumor cells, x100

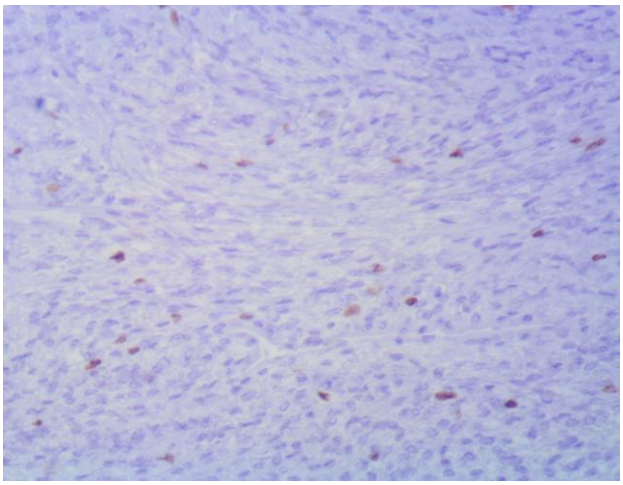

Fig. 5. Low proliferative index (Ki67, x100)

Discussion

The tumor may be grossly fibrous, myxoid, or even cystic. According to some researchers, the type and quantity of extracellular matrix correlate with the maturity of the lesion: an early lesion has a higher proportion of myxoid tissue, whereas an older lesion has a higher proportion of fibrotic tissue. Histopathologically, the tumor can be hypercellular and may imitate a sarcoma since it is made up of plump fibroblasts that are organized in short bundles and fascicles across a myxoid stroma. In other situations, there is greater fibrosis and reduced cellularity. In nodular fasciitis, there is no intralesional hemosiderin deposition [9]. Ultrasound can be helpful, but MRI is more accurate. There are a few diagnostic imaging publications detailing the MRI features of nodular fasciitis, despite the opinion that the disease diverse histologic features make its appearance on MRI nonspecific. According to Meyer *et al.* [10], who presented three cases, nodular fasciitis is typically well-defined. On T1-weighted imaging, their two mucoid and cellular intramuscular instances seemed slightly inhomogeneous and hyperintense to muscle tissue; on T2-weighted images, they appeared generally homogeneous with signal intensity greater than the fatty tissue. On all pulse sequences, the subcutaneous lesion, which had a fibrous histology, was hypointense. There was no perilesional tissue swelling. Meyer *et al.* concluded that the lesion's MRI appearance reflected its overall shape. The nodular fasciitis contrast-enhancing pattern was not described. Although rim enhancement was found [13-15], later reported cases demonstrated that the contrast-enhancing appearance of nodular fasciitis is typically homogenous [9,11,12].
There are several radiologic differential diagnoses for nodular fasciitis because its diagnostic signs are nonspecific. These include fibrosarcoma, sarcoidosis, dermatofibroma, neurofibroma, aggressive fibromatosis, neuroma and malignant fibrous histiocytoma. Fine-needle aspiration and histologic features may correlate well [16], but biopsy is typically necessary for a conclusive diagnosis.
Excision is the basis of therapy, while some researchers have also recommended monitoring [17] and corticosteroid injections in the tumor [18]. Relapse of the lesion is extremely uncommon, occurring in 1-2% of patients, and is frequently discovered shortly after excision [1,19,20].
There are a few clinical and radiologic characteristics that make the diagnosis of nodular fasciitis less likely: lesions in patients over 70 years old, tumors in the hand or foot, more than one lesion or tissue edema around the tumor; deposition of hemosiderin in the lesion seen on MRI and lesions that reoccur. The main concern is the similarity in clinical presentation and microscopic appearance between nodular fasciitis and sarcoma [12,21,22].

Conclusion

Nodular fasciitis needs to be recognized since, due to its rapid growth, rich cellularity, strong mitotic activity, and loosely confined form, it is sometimes mistaken as a sarcoma. Further research is required to establish the disease benign nature because large lesions are sometimes misinterpreted for malignant lesions. To overcome the difficulties of diagnosing nodular fasciitis, magnetic resonance imaging is required in addition to histology and immunohistochemistry. In any case, careful clinical follow-up is essential.

Conflict of interest statement. None declared.

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ММР

Case report

MULTIPLE PRIMARY MELANOMAS: A CASE REPORT

МУЛТИПЛИ ПРИМАРНИ МЕЛАНОМИ: ПРИКАЗ НА СЛУЧАЈ

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Abstract

Introduction. Patients diagnosed with single primary melanoma of the skin have an increased risk of developping other malignances, particularly other melanomas and non-melanoma skin cancers. Review of literature shows that most patients with multiple melanoma lesions develop only two melanomas, although patients with 3 or 4 lesions are also not uncommon.
Case report. A case of a 46-year-old woman with diagnosed 10 primary melanomas and 2 basal cell carcinomas (BCC) is presented. The patient came to the University Clinic for Plastic and Reconstructive Surgery in Skopje for a second opinion two months after a nodular melanoma on her left arm had been excised. As part of the regular monitoring schedule, dermoscopy examination recognized 9 other pigmented lesions as melanoma lesions and excisional biopsy was advised. The histopathological result revealed 9 primary melanomas and 2 BCC.
Discussion. Nodular melanoma is most frequently seen as the first described melanoma. The subsequent melanomas are usually thinner in terms of Breslow thickness and Clark's level. The first diagnosed melanoma in this case report was also nodular melanoma and the subsequent melanomas were thinner. There were no signs of lymphovascular invasion with in the initial tumor and brisk and non-brisk presence of tumor infiltrating lymphocytes (TIL) was observed. All of this is in accordance with literature data.
Conclusion. It is important to highlight the signifycance of the screening programs for early melanoma detection together with regular self-examination and preventive behavior. Early tumor detection is vital for decline in melanoma morbidity and mortality.

Keywords: skin melanoma, multiple primary lesions

Апстракт

Вовед. Пациентите со дијагностициран примарен меланом на кожа имаат зголемен ризик за развој на други малигноми, особено меланоми и не-меланомски кожни карциноми. Прегледот на литература покажува дека повеќето од пациентите со мултипли меланомски лезии имаат по две, три или четири лезии.
Приказ на случај. Прикажан е случај на 46 годишна жена со дијагностицирани 10 примарни меланоми и два базоцелуларни карциноми. Пациентката се јави на Клиниката за Пластична и реконструктивна хирургија во Скопје за второ мислење откако и бил дијагностициран и опериран нодуларен меланом на левата надлактица. Како дел од рутинските иследувања, направена е дермоскопија која посочи 9 други пигментни лезии сомнителни за меланоми. Промените се отстранети, а патохистолошкиот резултат покажа постоење на уште 9 примарни меланоми и два базоцелуларни карциноми.
Дикусија. Нодулареният меланом најчесто се јавува како примарната лезија, додека следно откриените меланоми се обично потенки земајќи ги во предвид класификациите на Бреслов и Кларк. И во овој приказ на случај, првиот откриен меланом беше нодуларен, додека останатите лезии беа потенки. Не беше забележана лимфоваскуларна инфилтрација, а беше забележана силно и умерено изразена лимфоцитна инфилтрација околу секоја од отстранетите меланомски промени. Сите податоци се во согласност со податоците од литературата.
Заклучок. Раното откривање на меланомот е крупцијално за намалувањето на неговиот морталитетот и морбидитет. Затоа е важно е да се потенцира значењето на скринингот во рано откривање на меланомот заедно со свесноста за само-преглед и превентивното однесување.

Клучни зборови: меланом на кожа, мултипли примарни лезии

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Introduction

Melanoma of the skin accounts for about 10% of all skin cancers. It is mainly caused by UV light-induced DNA damage with intense intermittent exposure at an early age, which has a very strong harmful effect. A personal history of dysplastic nevi syndrome is another well-known risk factor [1-2].
Melanoma patients are mainly concentrated in highly developed countries. They have lighter skin and thus greater susceptibility to ultraviolet radiation. The highest incidence has been observed in Australia and New Zeeland followed by Western Europe, North America and Northern Europe [3-4].
Patients diagnosed with single primary melanoma of the skin have an increased risk of developing other malignances during their lifetime. They are especially susceptible for developing multiple primary melanomas and non-melanoma skin cancers (NMSCs) [2,5].
Multiple primary melanomas are defined as more than one synchronous or metachronous melanoma in the same individual. Synchronous melanomas are distinct melanoma lesions discovered within three months after the diagnosis of the first melanoma. Some of them can be detected during a single visit at the doctor's office while others can be detected during the follow-up period.
According to different population-based studies, the incidence of multiple primary melanomas in melanoma patients with focus on cutaneous melanomas ranges from 2 to 10%. Synchronous lesions are discovered in 26-40% of the cases while the remainder of the lesions develops as metachronous. Almost half of the subsequent cutaneous melanomas are diagnosed in the first three years after the initial melanoma diagnosis [2,5-6]. However, cases with subsequent melanomas are reported up to 2 to 3 decades after the first lesion.
Etiological factors responsible for developing of a subsequent melanoma can be grouped into host-related, lifestyle factors and environmental influences. These factors include older age, fair skin type, male sex, family and personal history of melanoma, dysplastic nevi syndrome and multiple cherry angiomas [7-9]. The pathogenesis of cherry angiomas and its association with skin tumors is not yet clearly known. The study of Pastor Thomas N *et al*. suggests that cherry angiomas might be a result of actinic skin damage in patients with some degree of genetic susceptibility, but their association with multiple melanomas should further be investigated.
Review of the literature shows that most patients with multiple melanoma lesions develop only two melanomas. Patients with 3 or 4 lesions are also not uncommon. Rare case reports or studies report patients with multiple primary melanomas. Cleason *et al.* in their study that included 12.152 patients in Western Sweden reported only one patient diagnosed with a total of 16 separate melanomas. However, a case of as many as 48 melanomas in one patient was reported in the literature [10].

Case report

A case of a 46-year-old woman with diagnosed 10 primary melanomas and 2 basal cell carcinomas is presented. The patient came to the University Clinic for Plastic and Reconstructive Surgery in Skopje for a second opinion two months after a melanoma lesion on the outer part of her left arm had been excised in another institution. The first melanoma lesion was seen as nodular melanoma with T4a tumor thickness. The patient had no positive family history of melanoma or history of immunosuppression. She had fair skin and high count of nevi all over her body.
As part of the regular monitoring schedule, she was advised to perform a full skin body check-up at the dermatology unit. Dermoscopy examination recognized 9 pigmented lesions as melanoma lesions and excisional biopsy was advised (Figure 1a-f).

Fig. 1a.

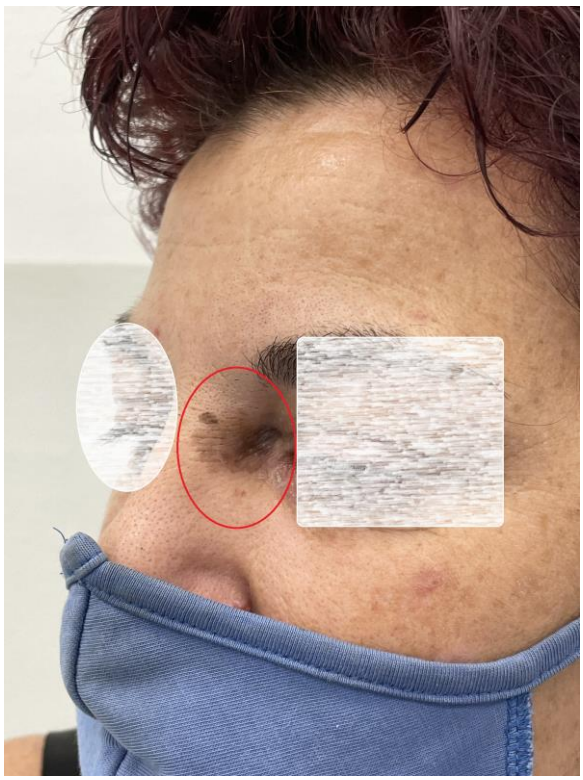

Fig. 1b.

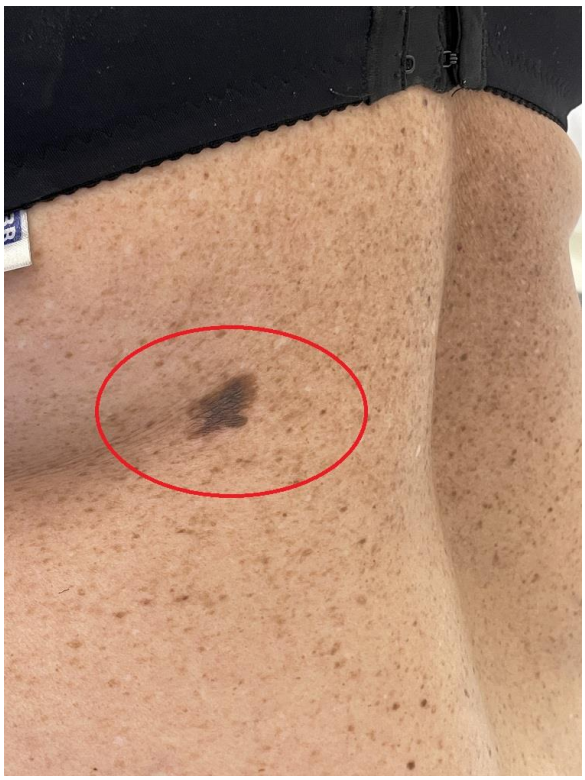

Fig. 1c.

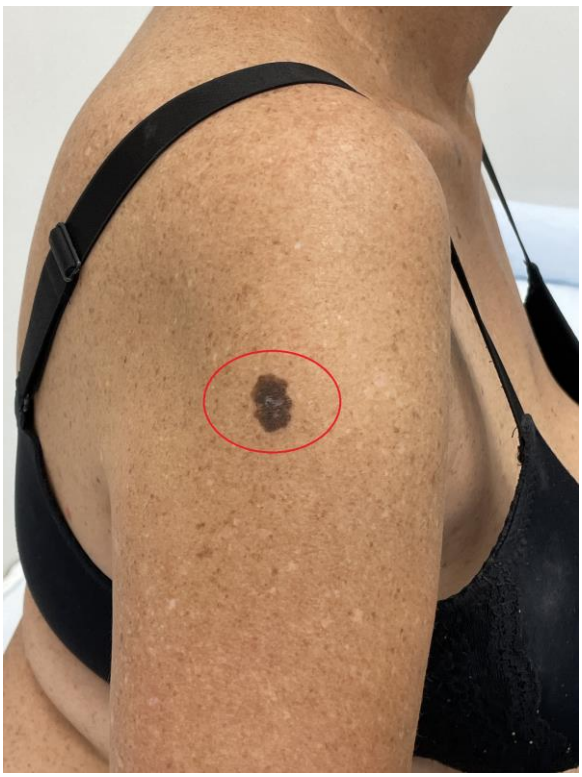

Fig. 1d.

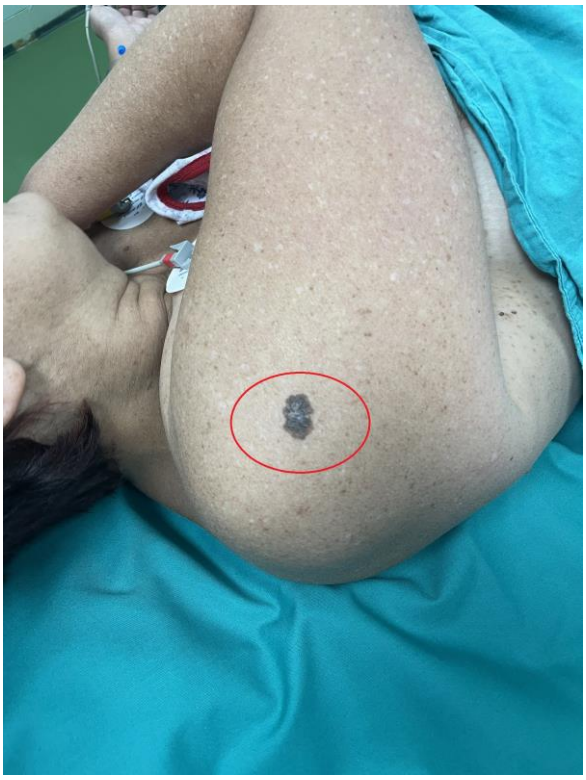

Fig. 1e.

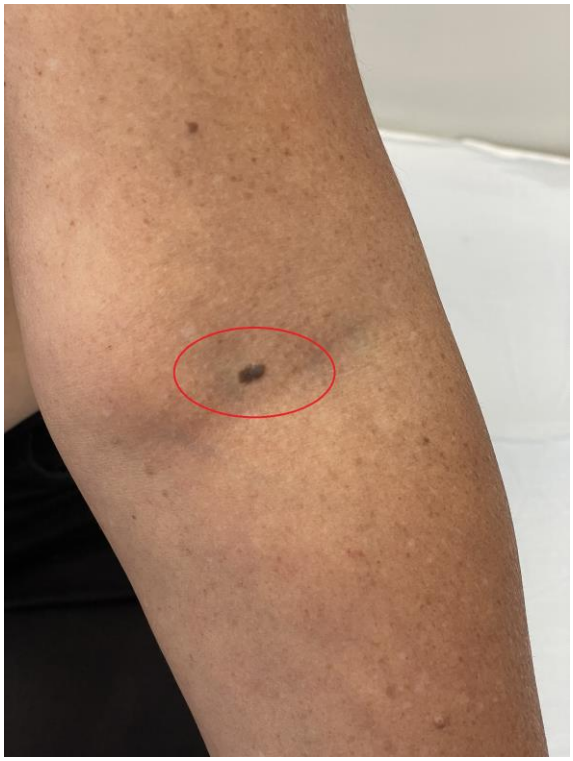

Fig. 1f.
Fig. 1a-f. Multiple primary melanomas in the presented patient

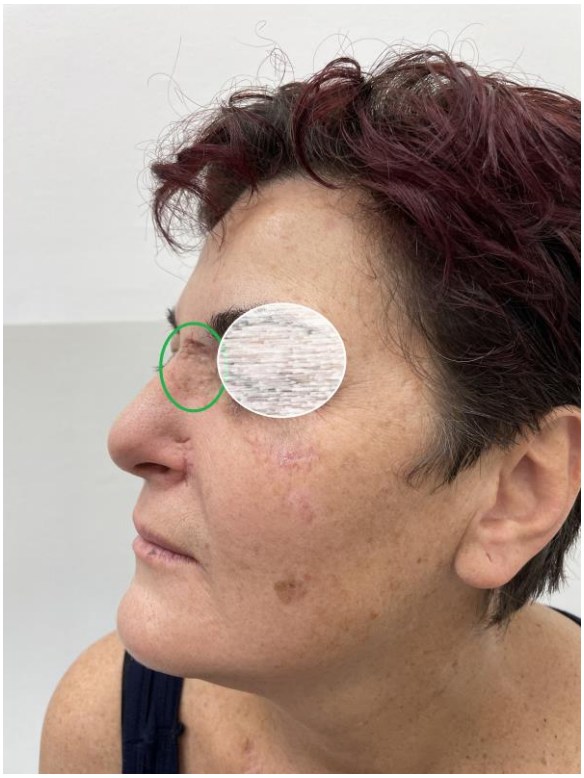

Fig. 2b.

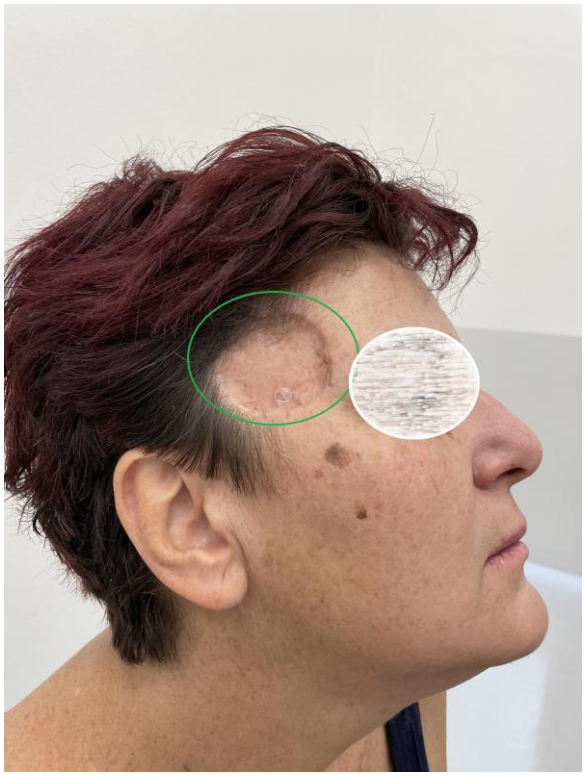

Fig. 2a.

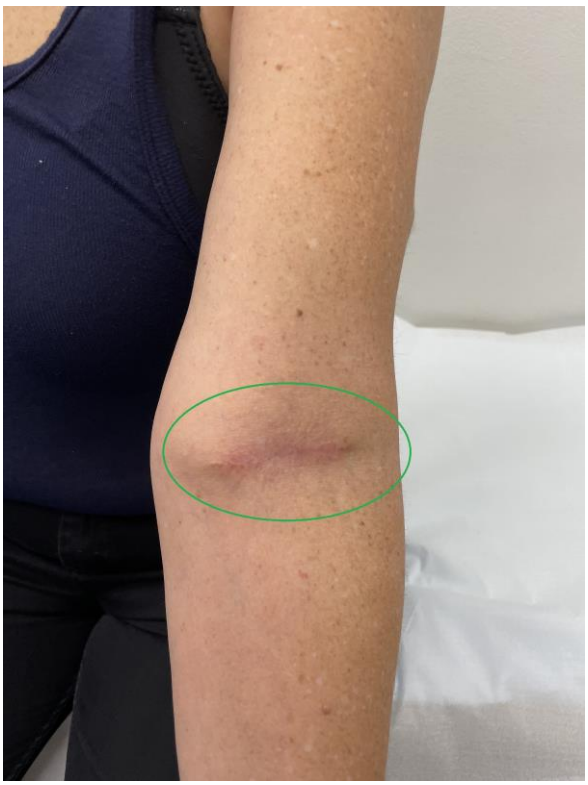

Fig. 2c.

Fig. 2a-c. Some of the defects after excision of melanoma were closed with direct suture while as the others were closed with split thickness skin grafts

The protocol of 2-stage treatment was described to the patient. Considering the need of two operations and having in mind her family obligations, a decision was made to perform a single, more radical operation of all the suspected lesions.

Radical excision of all the suspected melanoma lesions was performed with a safe margin ranging between 10-20 mm depending on the dermatological result, clinical finding and depending on where the lesions were located. The operation was performed in local potentiated anesthesia. Some of the defects were closed with direct suture while the others were closed with split thickness skin grafts [Figure 2a-c]. The postoperative period was uneventful. The patient was released on the 5th postoperative day. All the wounds healed with primary intention.

The histopathological result revealed 9 primary melanomas and 2 basal cell carcinomas. One of the melanoma lesions was described as superficial spreading melanoma (SSM) and another one was described as lentigo maligna melanoma (LMM). The rest of the lesions, seven, were diagnosed as non-otherwise specified melanoma lesions. The thickness of the tumors was varying between 3.2 mm and 0.3 mm. According to the TNM classification of cutaneous melanomas (UICC TNM 8), they were classified between T3a and T1a. No lymphovascular invasion was detected within any of the lesions, moreover brisk and non-brisk tumor infiltrating lymphocytes (TIL) presence around every tumor lesion was established respectively.

With regard to the anatomic side, 3 of the subsequent melanoma lesions were placed on the face; one was set on the neck whereas 3 melanoma lesions were found on the trunk and 2 on the upper extremities.

The performed PET scan showed no pathological accumulation. Afterwards she was treated with biological therapy (Pembrolizumab) at the Institute for Oncology. Eighteen months after the operation, her condition is stable and she is still on biological therapy.

Discussion

The presence of high count of dysplastic nevi is a well-recognized risk factor for developing multiple primary melanomas, which has also been shown in the presented case. Patients with single primary melanoma are prone to developing other malignances, especially multiple melanomas and non-melanoma skin lesions. The presented patient was diagnosed with 10 separate primary melanomas and two basal cell carcinomas.

Nodular melanoma is most frequently seen as the first described melanoma. The subsequent melanomas are usually thinner in terms of Breslow thickness and Clark's level of invasion. SSM together with LMM are the most common histological subtypes with subsequent melanomas. The first diagnosed melanoma in this case report was nodular melanoma as well. The other diagnosed melanomas were thinner. One of them was described as SSM and another one as LMM.

LMM usually occurs on sun damaged skin, hence, it is found more often on the sun exposed body parts. On the other hand, SSM occurs most often on the trunk and lower extremities. In the case presented here, the SSM lesion was set on the body (infraclavicular region) while the LMM lesion was set on the face, a fact which is in accordance with literature data.

Even when invasive, the second and high-order melanomas in MPM patients are usually thinner than the primary ones [11]. It has also been observed that these melanomas have negative sentinel lymph nodes and lack lymphovascular invasion with the initial tumor [5, 12]. This might be a result of both the biological tumor behavior and improved surveillance.

In this case report, no signs of lymphovascular invasion within the initial tumor were noticed and there was no non-brisk and brisk presence of TIL.

Most existing literature suggests that patients with MPMs have enhanced survival compared to patients with single primary melanoma [10,13]. This may be due to the "immunization effect" to common melanoma tumor agents. Namely, it has been suggested that patients who have had a melanoma may develop increased immunity against certain antigens expressed by tumor-associated melanocytes, and thus, the host immune response can result in slower tumor progression [14,15].

Conclusion

SSM together with LMM are the most common histological subtypes with subsequent melanomas. Since LMM is considered to be related with a high degree of cumulative exposure to UV radiation, active preventive measures against chronic sun damage should be stressed in patients with MPMs.

Furthermore, as 26-40% of the melanomas develop as synchronous lesions and might be discovered during a single visit at the attending doctor, it is imperative to underline the importance of a complete skin examina-

tion during the initial examination with a particular attention on chronically sun-exposed areas. On the other hand, the risk of developing subsequent primary melanomas remains increased for at least 20 years after the primary lesion, which leads us to the need of lifetime clinical follow-up.

The cutaneous melanoma incidence may be increasing at an exponential rate worldwide. If 2020 rates continue, the burden from melanoma is estimated to increase to 510,000 new cases (a roughly 50% increase) and to 96,000 deaths (a 68% increase) by 2040 [16]. That is why it is important to highlight the significance of the screening programs for early melanoma detection together with regular self-examination and preventive behavior. Early tumor detection is vital for decline in melanoma morbidity and mortality, thus decreasing the burden to the health system as well.

Conflict of interest statement. None declared.

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MMP

Case report

NECROTIZING FASCIITIS AFTER CAESAREAN SECTION – PRESENTATION OF TWO CASES

НЕКРОТИЗИРАЧКИ ФАСЦИИТИС ПО ЦАРСКИ РЕЗ - ПРЕЗЕНТАЦИЈА НА ДВА СЛУЧАЕВИ

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Abstract

Necrotizing fasciitis is a rare, but serious soft tissue infection. It spreads extremely quickly, progresses with serious complications in a short period and can cause death. Accurate diagnosis, timely antibiotic treatment and a surgical approach to the treatment are important in its timely resolution. It is characterized by rapid progressive necrosis of the subcutaneous tissue and fascia. Necrotizing fasciitis is described by the appearance of severe pain at the operative site, crepitations, hard induration of the subcutaneous tissue, bullous lesions, skin necrosis and ecchymosis.

In this paper, we present two isolated cases of necrotizing fasciitis in female patients delivered with Caesarean section. Female patients aged 35 and 26 came to our Clinic for Gynecology and Obstetrics for delivery. Both patients were without previous childbirths and without past illnesses. The only risk factor present was obesity. Both pregnancies went well and without complications.

Clinical diagnosis and the doctor's focus must remain at the highest level, despite the rarity of the diagnosis, because early, timely diagnosis is of crucial importance. Early aggressive debridement of any necrotic tissue is the cornerstone of treatment and the beginning of series of debridement that offer the highest chance of survival.

Keywords: necrotizing fasciitis, infection, caesarean section, childbirth, soft tissue infection

Абстракт

Некротизирачки фасциитис е ретка, но сериозна инфекција на меките ткива. Таа се шири исклучително брзо, напредува со сериозни компликации за краток период и може да предизвика смртен исход. Точната дијагноза, навремениот антибиотски третман и хируршки пристап кон третманот се важни во нејзиното навремено решавање. Таа се карактеризира со брза прогресивна некроза на поткожното ткиво и фасцијата. Некротизирачкиот фасциитис се опишува со појава на силна болка на оперативното место, крепитации, тврда индурација на поткожното ткиво, булозни лезии, кожна некроза и екхимоза.

Во овој труд ќе прикажеме два изолирани случаи на некротизирачки фасциитис кај пациентки, породени со Царски рез. Пациентки на 35 и 26 годишна возраст се јавиле на нашата Клиника за гинекологија и акушерство, за породување. Обете пациентки без претходни раѓања и без минати заболувања. Единствен ризик фактор присутен кај обете пациентки е обезноста. Двете бремености поминале во добар тек и без компликации. Клиничкото дијагностицирање и фокусот на докторот мора да остане на највисоко ниво, и покрај реткоста на дијагнозата, бидејќи раната, навремена дијагноза е од крucијално значење. Раниот агресивен дебридман на кое било некротично ткиво, го формира темелот на третманот и почетокот на серијата дебридмани, кои нудат највисока шанса за преживување.

Клучни зборови: некротизирачки фасциитис, инфекција, Царски рез, породување, инфекција на меки ткива

Introduction

Childbirth by Caesarean section is one of the most common surgical interventions in our country. Postpartum surgical infection and wound infection are the most common reasons for prolonged hospitalization and

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represent a great burden on the health insurance fund, the clinics, the health personnel and patients themselves.
Necrotizing fasciitis is a rare but serious soft tissue infection. It spreads extremely quickly, progresses with serious complications in a short period and can cause death. Accurate diagnosis, timely antibiotic treatment and a surgical approach to the treatment of the infection are key in its timely resolution [1].
Necrotizing fasciitis, which occurs after delivery with Caesarean section is an extremely rare occurrence. Many factors have been described for soft tissue infections.
On the maternal side: smoking, limited access to medical care, obesity, use of corticosteroids, nulliparity and twin gestations. Intrapartum and operative factors: premature rupture of membranes, prolonged ventilation, especially in the second stage of labor, long incision length, thickness of subcutaneous tissue >3 cm, subcutaneous hematoma, lack of antibiotic prophylaxis, emergency ventilation and excessive blood loss [2].
Effective interventions to reduce surgical site infections include antibiotic prophylaxis, preparation of the skin for surgery with chlorhexidine instead of iodine, vaginal cleansing with povidone-iodine, removal of the placenta with the umbilical cord instead of manually, using hypodermic sutures for thickness of the subcutaneous tissue >2 cm, wound closure with monofilament nonabsorbable sutures. Our Clinic has strict protocols and rules to prevent and spread intrahospital infections, and surgical wound infections.

Epidemiology

Wound complications

Wound hematoma and seroma are collections of blood and serum, respectively. Hematomas are usually due to failure of primary hemostasis or a bleeding diathesis such as anticoagulant therapy. Strong coughing or hypertension immediately after surgery can contribute to hematoma formation. Wound hematoma or seroma is described in 2-5% of women giving birth with Caesarean section and may be the cause of wound dehiscence and subsequent infection [3].
Wound infection presents with erythema, discharge, induration of the incision and generally occurs 4-7 days postoperatively. When the infection develops in the first 48 hours, usually the causative agents are *Streptococcus spp*. from group A and B. Other common pathogens are: *Ureaplasma urealyticum*, *Staphylococcus epidermalis*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis* [4].

Necrotizing fasciitis

Necrotizing fasciitis is a rare, serious infection that causes significant postpartum morbidity with Caesarean section. It is characterized by rapid progressive necrosis of the subcutaneous tissue and fascia. Necrotizing fasciitis is described by the appearance of severe pain at the operative site, crepitations, hard induration of the subcutaneous tissue, bullous lesions, skin necrosis and ecchymosis. The most important characteristic of this infection, which distinguishes it from other infections, is the extremely fast development and the importance of an immediate response. Computed tomography or magnetic resonance imaging confirm the diagnosis, showing signs of infection that has spread to the peritoneum and rectal muscles. Type I necrotizing fasciitis results from a polymicrobial infection that includes aerobic and anaerobic bacteria; Type II necrotizing fasciitis is generally caused by a single pathogen, group A streptococcus [5].

Case report

In this paper, we present two isolated cases of necrotizing fasciitis in female patients delivered with Caesarean section. Female patients aged 35 and 26 came to our Clinic (35-year-old patient, Patient A, and 26-year-old patient, Patient B).
Both patients were without previous childbirths and without past illnesses. The only risk factor present in both patients was obesity. Both pregnancies went well and without complications. They gave birth to healthy children with an Apgar score of 8/9.
During hospital treatment, they received a standard therapy with antibiotics, analgesics, NSAIDs, fluid therapy, antiaggregant and gastroprotective therapy. The postoperative course went smoothly, after which they were discharged for home treatment. Patients came for an examination after 7 days (A) and 10 (B) days, with pain in the operative wound, elevated body temperature up to 38 ˚C, tachycardia, with a feeling of weakness and nausea. Local examination showed erythema above and below the surgical incision; a hematoma was present in both patients with a diameter of 7 cm (A) and 3 cm (B).
In patient B, a bulla was present above the hematoma. Surrounding region was red, warm and indurated, painful to palpation. From the wounds, a seropurulent bloody content was drained, which had a distinct foul smell. The patient was admitted to the hospital for further treatment. Laboratory findings taken on the day of admission went in favor of a systemic infection.

Table 1. Laboratory findings of patients on readmission to the hospital

	Patient A	Patient B	Lab. results
wbc	14.51	11.7	[4-10]x10^9/L
hgb	108	83	120-180 g/L
hct	0.320	0.231	0.350-0.550 L/L
plt	265	110	[150-450]x10^9/L
crp	272	317	< 5 mg/L
d-dimer	3559	2656	[0-500] ngr/mL

Swabs were taken from the operative wound, vaginally and cervically. Computed tomography scans of the abdomen and small pelvis were performed. Emirian double antibiotic therapy was started with amp. Cephtriaxon a 2 gr s.1x1 and amp. Metronidazol a 0.5 gr s.3x1, as well as with antiaggregation therapy with amp. Clexane a 0.6 s.1x1. Primary therapy included fluid rehydration, analgesic and gastroprotective therapy.
Description of computed tomography of the abdomen and pelvis: abdominal organs with a normal morphology, passable and without signs of the presence of an abscess. A defect was noted on the anterior abdominal wall at the level of the small pelvis, which protruded to the peritoneum, but did not penetrate it. The fascia was thickened, and the subcutaneous fat, cloudy with air inclusions present and signs of necrosis. The uterus was enlarged and with a slight local reaction, post-operative condition; both adnexa normal, without free fluid in the pouch of Douglas.

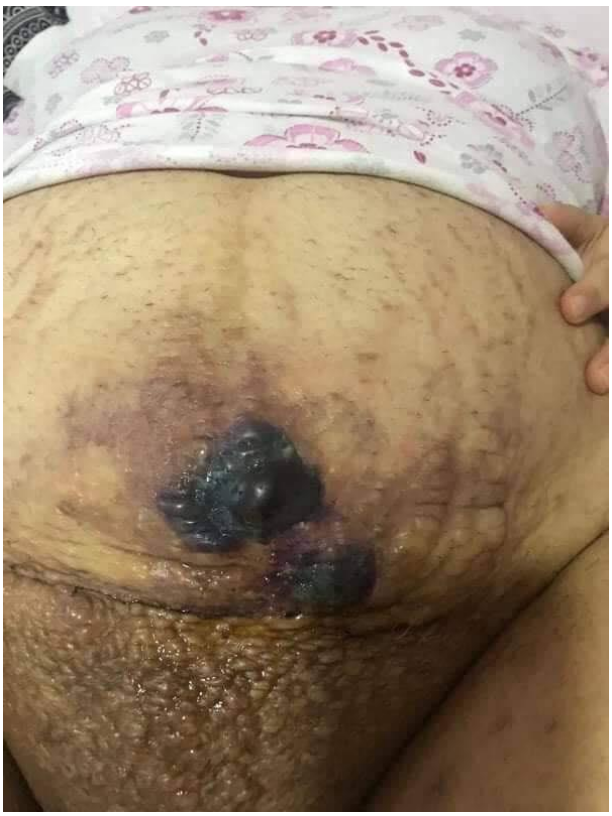

Fig. 1. Photograph of the wound on the day of readmission (patient A)

Results of the obtained swabs. The swabs from the vagina and cervix in patient A were negative for pathogens and noted the absence of normal flora, while in patient B the vaginal swab was positive for *Enterococcus* and *Escherichia coli*.
Result of a wound swab in patient A – *Enterococcus spp*. and patient B – *Streptococcus agalacticae* gr. B.
Colleagues from the Clinic for Plastic Surgery were

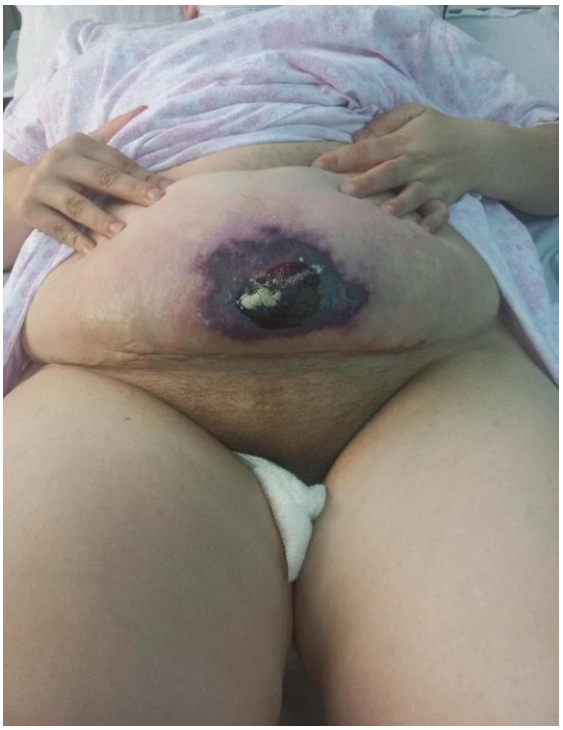

Fig. 2. Photograph of the wound on the day of readmission (patient B)

invited for consultation, examination and opinion on further treatment. An incision was made and the wound was washed abundantly with sol. NaCl 0.9%, sol. Betadine, sol. Hydrogen 3%, antiseptic Microdacyn. Clean ampoules of antibiotic Clindamycin and gauze soaked in hypertonic solution sol. NaCl 10% were applied locally. In the further treatment of the wounds, dressings with silver gauze, debridement and excision of the devitalized tissue were used.
Dressings were done daily, regularly, and this included vaginal douching. Amp. Vancomycin a 1 gr s.3x1 was included in both patients on the third day of hospitalization. During the hospital treatment, transfusion of blood derivatives was applied.
During the hospital stay, regular laboratory tests were performed every two days, and control swabs were taken on two occasions. When results from control swabs were negative, secondary closure was performed in both patients. The duration of hospitalization in the patients lasted about 1 month. Both patients were discharged in a good general condition, with negative smears and normal laboratory parameters.

Table 2. Laboratory findings of the patients at discharge from the re-hospital treatment

	Patient A	**Patient B**	**lab. results**
wbc	6.5	6.2	[4-10]x10^9/L
hgb	128	108	120-180 g/L
hct	0.39	0.33	0.350-0.550 L/L
plt	336	452	[150-450]x10^9/L
crp	17.5	12.6	< 5 mg/L
d-dimer	921.8	447	[0-500] ngr/mL

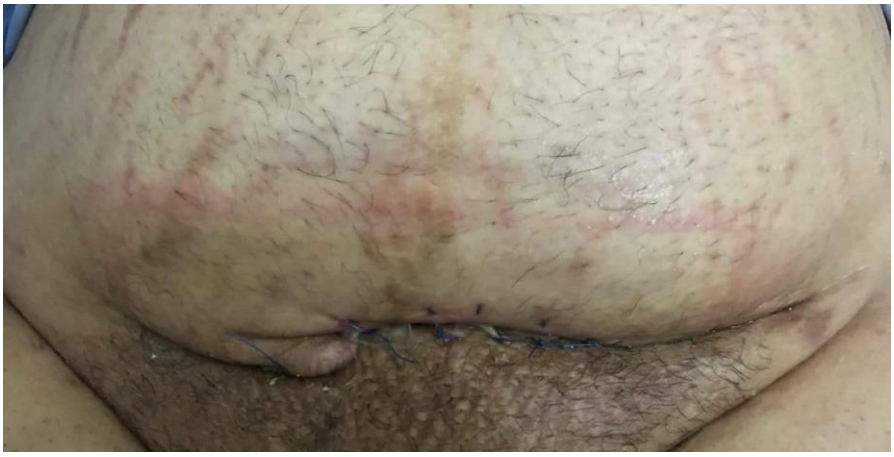

Fig. 3. Photograph of the wound on the day of discharge (patient A)

Discussion

Necrotizing fasciitis is a fulminant infection involving extensive areas of soft tissue necrosis, commonly involving the extremities, perineum, and abdominal wall. As in our cases, a minor penetrating injury or surgical incision is usually involved, with postoperative cases accounting for 20% of the total number of fasciitis cases.

While group A *Streptococcus* is the most common monomicrobial isolate, polymicrobial infections with a variety of Gram-positive, Gram-negative, aerobic, and anaerobic isolates can also occur. In our case we had *Enterococcus spp*., which is a Gram-positive coccus (normal for intestinal flora) and *Streptococcus agalactiae*, a beta-hemolytic Gram-positive coccus (the most common microbial pathogen in humans) [6].

The etiology of necrotizing fasciitis is not fully understood. Major risk factors include type 2 diabetes and age over 50 years, which are always associated with higher rates of morbidity and mortality. These factors were absent in our cases, but cases with necrotizing fasciitis have been reported after the use of NSAIDs (non-steroidal anti-inflammatory drugs) immediately after delivery with Caesarean section.

NSAIDs are associated with necrotizing fasciitis in a temporal manner. Controversial is the claim that NSAIDs only mask the primary signs and symptoms and delay the diagnosis of necrotizing fasciitis. Inhibition of granulocyte chemotaxis, phagocytosis, bactericidal activity and reduced lymphocyte transformation have been documented *in vivo* as a consequence of NSAID use in this type of patients [7].

Most patients have signs of inflammation such as erythema, swelling and pain at the infected site. Severe pain, which does not correlate with local findings and presents with a systemic infection, should direct our attention to the suspicion of necrotizing fasciitis.

The native graph of the abdomen in the standing position reveals the presence of gases in the muscles and superficial fat only in 35% of cases. Computed tomography is the diagnostic approach of choice. It helps us distinguish the involved structures, the type of infection and helps in the decision on further treatment. A normal finding on computed tomography, on the other hand, does not exclude the diagnosis. Despite patients' unstable condition, surgical debridement should be done continuously and not delayed until the condition is stabilized.

It is important to note that serial debridements are required and that fascial closure is not recommended after the first debridement. Leaving the abdomen open as in these two cases is consistent with infection control techniques and prevention of abdominal compartment syndrome. With serial debridements and regular dressings, the final defect that needs to be reconstructed is reduced over time. After obtaining two consecutive negative wound swabs, and granulation tissue present, we performed a final dressing and closure of the fascia and superficial skin layers [8].

Conclusions

Postpartum necrotizing fasciitis remains a rare challenge, with high mortality. The rapid deterioration of the condition in both patients with septic shock and multisystem organ failure could result in death. Clinical diagnosis and the doctor's focus must remain at the highest level, despite the rarity of the diagnosis, because early, timely diagnosis is of crucial importance. Early aggressive debridement of any necrotic tissue is the cornerstone of treatment and the beginning of a series of debridements that offer the highest chance of survival.

Conflict of interest statement. None declared.

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ММР

Case report

ADULT PATIENT WITH BRONCHOGENIC CYST - A RARE PULMONARY DEVELOPMENTAL ANOMALY

ВОЗРАСЕН ПАЦИЕНТ СО БРОНХОГЕНА ЦИСТА - РЕТКА АНОМАЛИЈА ВО РАЗВОЈОТ НА БЕЛИТЕ ДРОБОВИ

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Abstract

Bronchogenic cysts are anomalies in the prenatal development of the lungs that we encounter extremely rarely in the adult population because they are diagnosed in childhood, usually after birth. So far, there is no published case in the Republic of Macedonia with a diagnosed bronchogenic cyst in the lung parenchyma. Such cases need to be solved with surgical intervention in order to avoid possible complications.

Keywords: bronchogenic cyst, adults, parenchymal, mediastinal

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Апстракт

Бронхогените цисти се аномалии во пренаталниот развој на белите дробови, кои ги среќаваме исклучително ретко кај возрасната популација бидејќи се дијагностицираат уште во детска возраст, најчесто уште по раѓањето. Досега не е објавен случај во Р. С. Македонија со дијагностицирана бронхогена циста во паренхимот на белите дробови. Ваквите случаи потребно е да се решаваат со хируршка интервенција, со цел да се избегнат можните компликации.

Клучни зборови: бронхогена циста, паренхимална, мадијастинална, возрасни

Introduction

Congenital abnormalities of respiratory organs are structural and partly functional disorders. The respiratory system develops continuously from the embryonic period to the postnatal human life. The development of the respiratory system takes place in three phases: glandular phase, canalicular phase and alveolar phase. The glandular phase, which lasts until the 16th week of the prenatal period, is characterized by the development of airways and blood vessels. In the second canalicular phase, the peripheral part of the bronchial stem and the pulmonary acini develop and this period lasts until the 24th week of prenatal development. Then the development continues until the end of the intrauterine life until the 8th year of life with the development of the alveoli in the third-alveolar phase. Numerous etiological factors such as viruses, irritation, drugs, and unknown environmental factors can lead to developmental abnormalities of the respiratory system.

Bronchogenic cysts occur as a result of abnormal development of the primitive tracheobronchial tube during the prenatal period. The location of the bronchial cysts can vary, depending on the period when it occurs. If it occurs earlier in the embryonic period, its location is usually mediastinal while a later appearance of the cyst often results in its location in the pulmonary parenchyma [1]. Studies suggest that mediastinal bronchogenic cysts are most common, appearing in 65–90% of cases. Bronchogenic cysts located in the pulmonary parenchyma are extremely rare and if accompanied by any complications, they may pose a significant differential diagnostic problem. A safe diagnosis can only be made via histopathological examination, i.e., complete surgical excision of the bronchial cyst.

Case report

We present a 72-year-old patient, a longtime smoker, who occasionally consumed alcohol. He was hospitalized due to symptoms of cough with purulent sputum, elevated temperature (up to 38C), pain in the lower left hemithorax, sore throat, fatigue, malaise, starting 7 days before admission to the hospital. The patient provided data on cardiological comorbidities (PCI/Stenting

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four years ago, placement of two-electrode heart electro stimulator), a stomach ulcer diagnosed 6 years ago.
Clinical presentation and diagnostic procedures: In the patient's examination of the auscultation of the lungs, pulmonary crackles were present poster basally on the left side. Laboratory analyses showed leukocytosis with neutrophilia $16.7x10^9$ /L (reference value: 4.0-$10.0x10^9$/L), procalcitonin: 0.167 ng/ ml (where normal value is below 0.05 ng/ml), sedimentation rate: 52 (reference value: 0-20) (Table 1).

Table 1. Results of laboratory analyses

Tests	Result	Reference values
Sedimentation rate	52	0-20
Erythrocytes (RBCs)	4.8 x 10^{12}/L	4.6-6.2 x 10^{12}/L
Hemoglobin (Hb)	152 g/L	140-180 g/L
Hematocrit (HCT)	0.42	0.37-0.54
Mean corpuscular volume (MCV)	84 fL	82.0-98.0 fL
Leukocytes (WBCs)	16.7 x 10^9/L	4-10 x 10^9/L
Lymphocytes	15.3%	15-50%
Neutrophils	82.6%	35-80%
Mixed cell count	2.1%	2-15%
Platelet count (PLT)	167 x 10^9/L	150-450 x 10^9/L
Procalcitonin	0.167 ng/ml	<0.05 ng/ml

Microbiological analysis of sputum isolated *Staphylococcus aureus* - methicillin resistant. Three specimens of sputum, with fluorescent microscopy, did not isolate acid-resistant bacteria. X-ray of the lungs showed the presence of a solitary oval mass with a diameter of approximately 5 cm located in the lower left lobe.
A computed tomography (CT) of the lungs (Figure 1) showed an intraparenchymal oval substrate with dimensions of 41x47 mm in the posterior part of the lower left lobe, with a mixed density, and a predominantly thick liquid content, as well as a probable blood content, which was not colored after the contrast was given. The change corresponded to a cystic nature, with thin walls, well separated from the surrounding pulmonary parenchyma and with benign aspect on CT. A hydatid cyst could also be suspected.

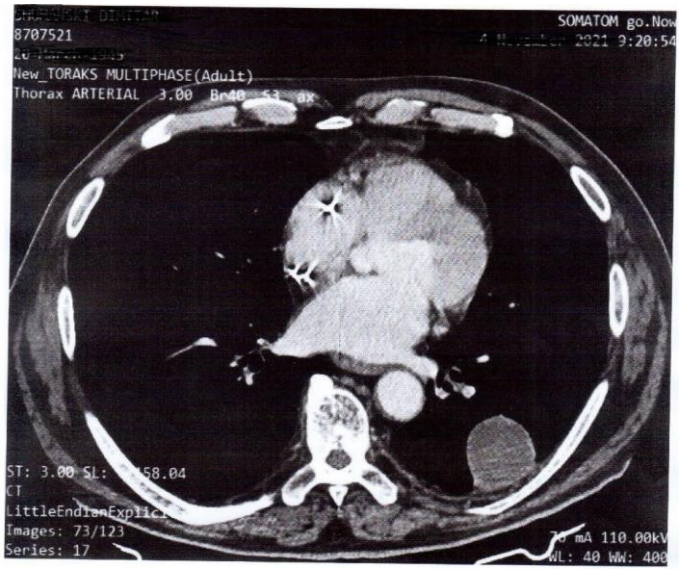

Fig. 1. Computerized lung tomography: a substrate with cystic nature, with thin walls, well separated from the surrounding pulmonary parenchyma and with benign aspect

Table 2. Diagnostic Testing Methods

Testing Method	Specimen	Result
Bacterial culture	Sputum	Staphylococcus aureus-methicillin resistant
Mycobacterial culture	Sputum	Negative for acid-resistant bacteria
Indirect hemagglutination test against *Echinococcus granulosus*	Serum	Negative titer of *Echinococcus*
Quantitative test for the detection of antibodies against *Echinococcus granulosus*	Serum	Negative

An indirect hemagglutination test showed a negative titer of *Echinococcus*. A quantitative test for the detection of antibodies against *Echinococcus granulosus* also came out negative. Because of the isolated bacteria from the sputum culture, an antibiotic therapy was started, corresponding with the antibiogram (Table 2).
Then, a bronchoscopy was performed showing complete passability of the bronchi (up to the subsegments). A transbronchial lung biopsy (TBB) was also performed, and a histopathological result was established based on parts of the bronchial wall built from the bronchial cartilage, on which the swollen connective tissue was attached, with hyperplastic respiratory epithelium covering its surface, without any signs of atypia. Diffusely, a very discrete inflammatory infiltrate of lymphocytes could be seen, without the presence of neoplastic cells.
A CT-guided transthoracic lung biopsy was performed, with the goal of setting a concrete diagnosis, from which a histopathological result was gained showing no signs of neoplastic cells. After consulting a thoracic surgeon, a posterolateral thoracotomy was made, with a complete resection of the bronchogenic cyst. With the histological results from the postoperative sample, a definitive diagnosis of a bronchogenic cyst was established. The patient was discharged from the hospital on day 5, in a well general condition.

Discussion

The bronchogenic cysts can be diagnosed in children or in adult population, depending on the symptoms with which they are presented. Most often they appear in the mediastinal region, with an 80% possibility of appearance in this region. They also make up for about 5-15% of all abnormal mediastinal masses. They can also appear in the pulmonary parenchyma, especially in the later stages of life. Apart from these two regions, the bronchogenic cysts can be found in the abdomen [2]. In children, they can be asymptomatic for a long period of time, until the occurrence of symptoms such as difficulty breathing, anorexia, difficulty swallowing and other symptoms depending on the location. According to statistical data, about 70.8% of cases of bronchogenic cysts during childhood are accompanied by symptoms [3]. According to data from recent literature, most intrapulmonary cysts occur in the lower lobes of the lungs, but, although rare, a localization in the upper lobes can also appear [4-6]. The bronchogenic cysts can be asymptomatic for a long time and pose a serious threat because of the complications which they can give rise to, which can manifest as bleeding, ruptures, infections or compression of the surrounding organs [2]. Complications of bronchogenic cysts are not a rare occurrence. In fact, according to statistics, in 45% of cases these complications gain form in one way or another [4]. There is also the possibility of communication of the bronchogenic cyst with the airway, which can result in the appearance of air or hydro-air level, and in this situation the bronchogenic cyst acts as an abscess cavity. Present changes in the environment such as infections, other accompanying consolidations or atelectasis, can further complicate the diagnostic process. Complications such as pneumothorax, rupture of the bronchogenic cyst in the trachea or pericardial space have also been reported. Our case was an adult male, for whom diagnostic procedures were conducted, with determining the nature of the change that was visualized on the CT scan of the lungs as the goal. The results did not confirm the presence of a malignant transformation or a hydatid cyst. Because of this, surgical treatment was conducted on the change and the bioptic material alluded to elements typical of a bronchogenic cyst, more specifically a pseudostratified ciliated epithelium, smooth muscle tissue, cartilaginous tissue, as well as bronchial mucous glands. The CT scan of the lungs showed the bronchogenic cyst as being well separated, oval structure with a thin wall, with dense liquid content, even though the density can be higher depending on the possible following infection, presence of protein or calcium content [8,9]. In our case, a mixed density was present, with a predominantly dense liquid content which did not increase its density postcontrast and could not be dyed. Bronchogenic cysts in the lungs are especially important from a differential diagnosis perspective, because a large spectrum of changes could come in mind which need to be excluded from the definitive diagnosis with a certain number of diagnostic procedures [10]. In the case of parenchymal localization of the bronchial cyst, the differential diagnosis can refer to neoplasms, changes which are fungal in nature, a hydatid cyst, granulomas, infected bullae or caverns with a specific etiology. There is data which alludes to a malignant transformation of the bronchogenic cyst into a rhabdomyosarcoma, blastoma as well as a bronchoalveolar cancer in adults with a rate of 0.7% [11].

Conclusion

Experience shows that bronchogenic cysts are best treated with a surgical intervention, whenever possible [12]. Concrete diagnosis can be established only after complete excision of the bronchogenic cyst and when histological analysis is performed. Furthermore, the surgical treatment is also of significant importance, because it can contribute to evading a number of complications which can be caused by the bronchogenic cyst [13,14]. Surgical treatment of the bronchogenic cyst should not be delayed, because appearance of complications is deeply connected to the high rate of postoperative morbidity.

Conflict of interest statement. None declared.

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Case report

ARTERIAL THROMBOSIS IN A COVID-19 PATIENT

АРТЕРИСКА ТРОМБОЗА КАЈ ПАЦИЕНТ СО КОВИД 19

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Abstract

Arterial thrombosis is one of the complications descrybed in severe COVID-19. Our presented case had thrombosis of abdominal aorta and left renal artery despite prophylactic treatment with low molecular heparin - enoxaparine. Thrombotic lesions were defined with CT angiography. Treatment consisted of therapeutic doses of low molecular heparin and Bergman solution. After 42 day of hospital treatment, the patient was discharged and vascular surgeon consultations were performed. By presenting this case, we want to draw attention to the need for early diagnosis of this complication and to highlight the need for treatment with therapeutic doses of low molecular heparin in patients with severe Covid pneumonia or oxygen dependent patients and in risk for thrombosis.

Keywords: COVID-19, arterial thrombosis, heparin

Апстракт

Артериската тромбоза претставува една од компликациите опишувана при тешка форма на Ковид 19. Нашиот случај е презентиран со тромбоза на абдоминална аорта и тромбоза на лева бубрежна артерија. Дијагноза на тромботичните промени се потврди со КТ ангиографија. Третманот беше спроведен со тераписки дози на хепарин со ниска молекуларност-еноксапарин и раствор на Бергман. Пациентката се испишува по 42 дена на болничко лекување со препорака за понатамошно проследување од страна на васкуларен хирург. Со приказ на овој случај сакаме да осврнеме внимание на потребата за рана дијагноза на оваа компликација и да ставиме на виделина потребата за лекување со тераписки дози на нискомолекуларен хепарин кај пациенти со тешка Ковид пневмонија или кислородно зависни со ризик за развој на тромбоза.

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Клучни зборови: КОВИД 19, артериска тромбоза, хепарин

Introduction

Two years of clinical experience in a Covid-19 department showed us the importance of fast and timely diagnosis and treatment of different life-threatening complications in Covid-19 severe/critical illness. Thromboembolism as the most common urgent complication with the highest probability of evolving in the phase of the so known cytokine storm, taught us to be predicttive in taking proper steps in diagnosis and treatment. Successful treatment of the severe and critical COVID-19 disease requires a multidisciplinary approach.

The scientific data suggest that severe COVID-19 illness is associated with endothelial injury that leads to dysregulation of homeostasis and coagulopathy with the final result of immunothrombosis [1]. SARS-CoV 2 is a viral infectious disease that causes various manifestations and dysfunctions, including coagulopathy. Even though pulmonary thromboembolism is so far very often encountered in these patients, thrombosis in arterial blood vessels is also described, but rarely. In the everyday medical publications, we see information about thrombosis in different locations such as *truncus celiacus*, *arteria mesenterica superior*, *arteria renalis*, aorta etc. [3].

Case presentation

A 70-year-old woman with hypertension was admitted to our COVID department with a history of fever, malaise and cough during the past 7 days. Clinical examination on admission showed fever and rhonchi on pulmonary auscultation and O2 saturation of 88-89% on room air. PCR Covid swap resulted positive. Before admission, she had been treated during two days with antimicrobial therapy (Cefixime 400 mg once daily) and oral antiplatelet (Aspirin 100 mg once daily). Laboratory tests on admission showed mild lymphopenia, increased C-reactive protein levels, increased LDH and D-Dimer levels (Table 1). Chest x-ray (CXR) on

admission showed multilobar interstitial opacities (Figure 1A). The patient had a history of smoking and arterial hypertension treated with Enap 5 mg once daily. During the hospital stay, the patient was treated first with a combined parenteral antimicrobial therapy (third generation Cephalosporin (Ceftriaxone) - 2 g/daily, Quinolone (Ciprofloxacin) - 400 mg/twice daily), convalescent plasma substitution on the second day of treatment, anticoagulant therapy with low molecular heparin at a dose of 40 mg twice daily, oxygen supplementation with nasal cannula 3l/min. During the next five days of hospitalization, the patient continued to have persistent fever and an increase in oxygen requierements with non-rebreather mask (16l/min). CXR (Figure 1B) and CT thorax (Figure 1C, 1D) on day 5 of hospital treatment presented a rapid progression of opacities, and laboratory examinations showed an increase in acute inflammatory markers. Rales were noted on pulmonary auscultation on both sides.

Table 1. Laboratory test results

Variable	Reference	On admission	12th day of illness	16th day illness	19th day of illness	28th day of illness	30th day of illness	31st day of illness	43th day illness	50th day illness
Hb(g/l)	(115-180)	137	123	128	132	107	89	92	95	93
RBC (x10-3)	(4000-5500)	5160	4640	4940	4990	4020	3330	3430	3480	3460
WBC (x10-3)	(4.0-11)	5.2	5.4	18	15.5	14.2	14.2	9.1	7.5	6,1
Plat.(x10-3)	(150-400)	232	321	465	349	399	312	306	308	304
Hct	(41-50)	0.41	0.38	0.4	0.4	0.33	0.28	0.29	0.3	0,29
Ne	(0.25-0.70)	0.78	0.85	0.89	0.93	0.84	0.91	0.86	0.61	0,64
Ly	(0.21-0.25)	0.16	0.11	0.07	0.03	0.1	0.04	0.07	0.2	0,21
NLR		4.8	7.7	12.7	31	8.4	22.7	12.2	3	3
CRP(mg)	(0-10)	24	254	71	395	12		12	15	23
LDH(UI)	(120-246)	285	533	895	3578	1081	826		319	271
CK(UI/)	(30-170)	55	623	205	125	22	24	20	20	20
ALT(UI/)	(10-52)	42	46	59	312	147			49	34
AST (UI/ml)	(10-47)	49	72	55	312	49			19	15
Troponin (pg/ml)	(<34.2)				5,2	3.3	28.1	6,2		
ser.Fe ++(mmol/l	(12.5-26)			8.2		12.3			8.6	5.4
Glob. (g/l	(20-35)					26			23	
Glob. (g/l	(20-35)					26			23	
Alb (g/l	(34-54)					27			28	
tot.prot.(g/l)	(60-83)					53			51	

Hb-hemoglobine; RBc-red blood cells; WBC- white blood cells; Plat.-platelet count; Hct-hematocrit; Ne-neutrophiles; Ly-lymphocites; NLR-neutrophil/lymphocyte ratio; CRP- reactive protein C; LDH-lactat dehydrogenase; CK-creatin kinase; ALT-alanin aminotransferase; AST-aspartat aminotransferase; glob.-globulines; alb-albumines; tot.prot-total proteins

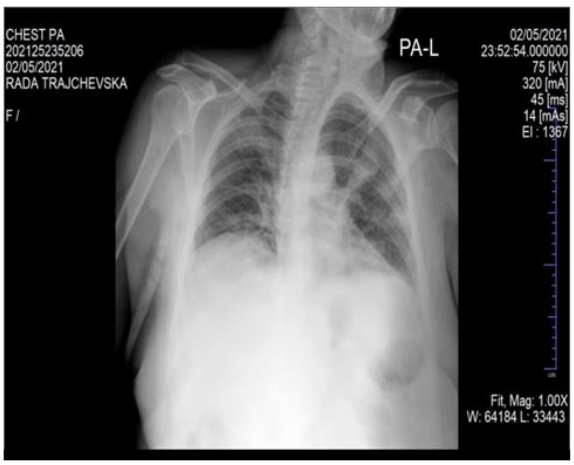

Fig. 1(A). CXR on admission

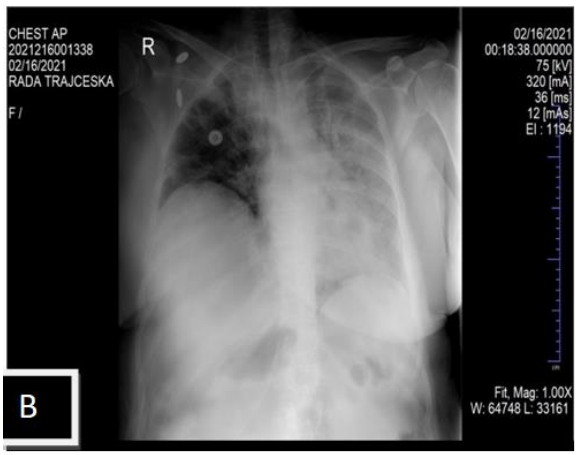

Fig. 1(B). CXR on 12th day of illness

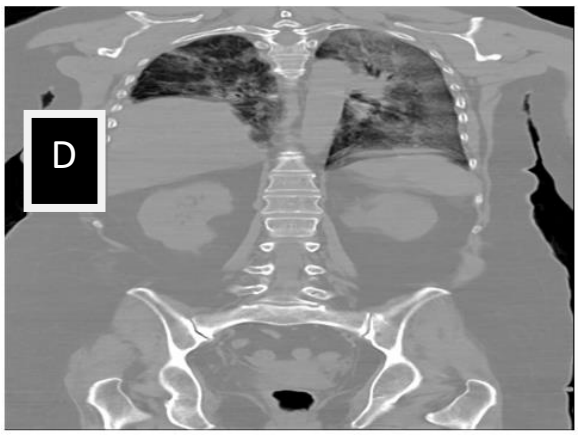

Fig. 1(C). Computed thomography of thorax billateral opacities

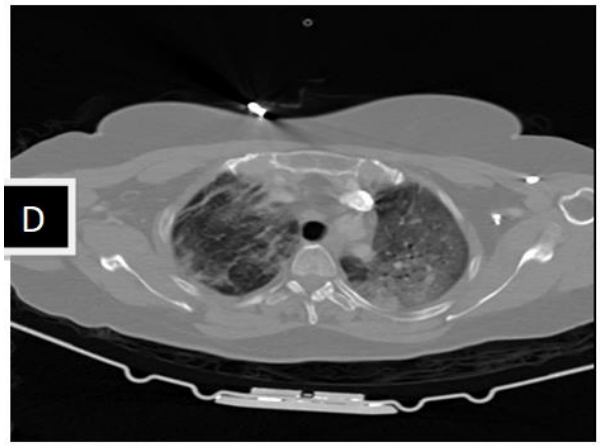

Fig. 1 (D). Ground glass images on CT

On day 12 of illness, treatment was complemented with Remdesivir parenterally (200 mg/24h the first day, continued with 100 mg/24h the next 4 days). In absence of other immunomodulators like tocilizumab or baricitinib, and taking into account high levels of inflammatory markers and increase on oxygen supplementation we started treatment with corticosteroids parenterally [8]. On day 10 of hospitalization (17^{th} day of illness) hemorrhagic diarrhea, abdominal pain and livid cold right foot were noticed. Microbiological testing-coproculture and C. difficille toxin resulted negative, in adverse stool blood test was positive. CT angiography of abdomen and thorax (Figure 2A, 2B, 2C) was obtained to define lesions and their etiology. The imaging showed thrombosis of abdominal aorta and left renal artery with consecutive infarction of the left kidney. Vascular surgeon preferred conservative treatment with therapeutic doses of low molecular heparin (Enoxaparine 80 mg/twice daily administered subcutaneously) and parenteral Bergman solution. We performed continuous examination of blood hemostasis and anti-Xa with proper corrections on dosage according to the results (Table 2). Following the treatment, two days later, symptoms had fast clinical resolution with regression of diarrhea and normal coloring of the right foot. On day 15 of treatment, the patient complained of severe chest pain.

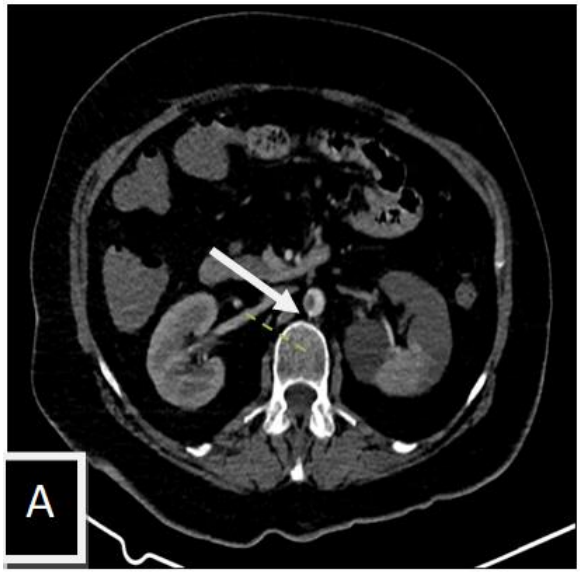

Fig. 2 (A). Thrombosis in abdominal aorta

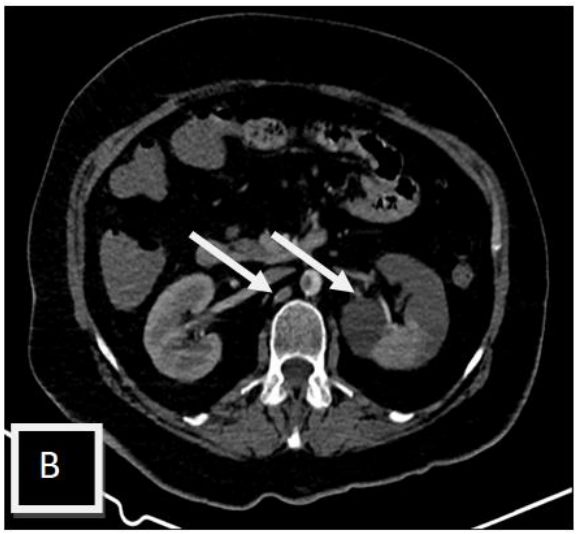

Fig. 2 (B). Thrombosis of left kidney artery

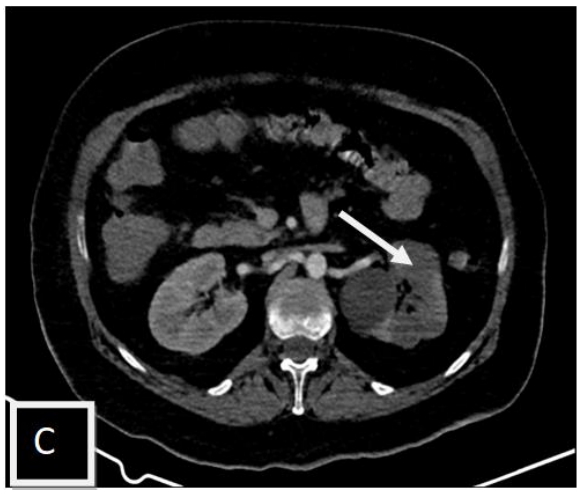

Fig. 2 (C). Consecutive infarction of left kidney

Cardiologic examination was performed including electrocardiogram (ST elevations, troponin levels 28.1 pg/ml..6.2 pg/ml). Conservative treatment with antiplatelet drugs (clopidogrel and aspirin) suggested by a cardiologist led to fast resolution of symptoms. During hospital stay, continuous clinical progression was observed and oxygen therapy was weaned off (oxygen saturation (SpO2) 92% on room air measured by pulse oxymeter) three days before release. The patient was successfully discharged on day 42, and vascular evaluation was continued. After 6 months, the patient was diagnosed with adenocarcinoma colon transversum, so surgical and oncological treatment is continued.

Table 2. Homeostasis and d-dimers

Variables	Reference	7th day of illnes	12th day of illness	16th day of illness	20th day of illness	25th day of illness	28th day of illness	31st day of illness	40th day of illness	before discharge
Plat.	**150-450**	**202**	**252**	**411**	**238**	**309**	**338**	**291**	**259**	**324**
Hct	**35-50**	**39.1**	**36.2**	**37.6**	**35.2**	**29.4**	**29.7**	**29.5**	**28.4**	**29.1**
PT	**9.8-14.2**	**12.8**	**11**	**11.8**	**11.5**	**11.56**	**12**	**11.2**	**10.83**	**10.5**
aPTT	**27.9-37.7**	**34.3**	**31.1**	**30.7**	**25.8**	**28.2**	**26.9**	**25.8**	**27.21**	**25**
TT	**16.1-22.2**	**17.9**	**17.3**	**20.9**	**18.9**	**25**	**22.2**	**22.5**	**24.59**	**18**
DD	**0-500**	**995.4**	**1626**	**2857**	**8867**	**1973**	**1392**	**1101**	**963**	**674**
anti Xa	**0.5-1.2**				**0.4**	**0.87**	**1.3**	**1.3**	**1.24**	
CLt	**0-106**				**57**	**76**				

Plat.-platelet count; Hct-hematocryt; PT- prothrombine time; aPTT- activated prothrombine time; TT- thrombin time; DD- d-dimers; CLt- clopidogrel test

Discussion

Nowadays, accumulated scientific data about the pathophysiology of SARS - CoV-2 as a viral infectious disease complicated with vascular disease injury suggest the hypercoagulability and immunothrombosis in the genesis of severe clinical features of COVID-19 [2]. Vascular thrombosis, much more venous than arterial, as a complication of the severe clinical form is often described in medical publications [3]. The cytokine storm as an exaggerated immune response to the virus leads to a hyperinflammatory process, hypoxia, diffuse intravascular coagulation and consecutive immobilization of patients [4]. In our case, thrombosis occurred in blood vessels with high flow. Some studies suggest that this is related with changes in platelet function found in COVID-19 patients [5]. It is suggested that this phenomenon occurs *in situ* rather than due to embolism. Prophylaxis with low molecular heparin in some cases does not stop the evolving immunothrombosis in patients with severe disease [6]. Some studies suggest that antiplatelet drugs may have benefit especially in long-term use before infection with SARS-CoV-2 [7]. Meizlish *et al*. suggest that retrospective data from patients who received Aspirin as an antiplatelet drug had lower mortality rate. Different approaches in various studies are evolved in the spectrum of dosage of low molecular heparin, but diagnosing thrombosis leads to the need of therapeutic antithrombotic dosage of low molecular heparin. In our everyday practice, patients with severe hypoxemia and a high risk of thrombosis are treated with therapeutic doses of low molecular heparin with final aim to reach therapeutic doses in blood and this is regularly controlled by checking anti-Xa levels. In patients with severe COVID-19 disease and high risk of thrombosis, we support usage of therapeutic doses of anticoagulant drugs with high precautions on possible complications [8,9].

Restrictions and limitations

In this case presentation, the limitations were no opportunity to examine interleukin 6, ferritin and fibrinogen levels. We also did not perform a control CT angiography to define the resolution of thrombosis and lesions, so the evaluation is based on clinical features. Antiviral treatment with Remdesivir was started on day 12th of illness due to technical problems even though it is recommended as soon as possible.

Conclusion

Patients with severe COVID-19 despite treatment with low molecular heparin are at high risk of thrombosis. Our patient was diagnosed early regarding onset of symptoms, and treatment with therapeutic doses of low molecular heparin- enoxaparine gave improving clinical results. So, this raises questions regarding treatment with therapeutic doses of low molecular heparin in patients who are treated in hospital conditions and who require oxygen supplemental therapy with high risk of trombosis, in adverse of prophylactic dosage.

Conflict of interest statement. None declared.

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УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед"(ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.
Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) listata na Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):
а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.
б) заеднички автор
GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.
в) ***без автор*** **-** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).
г) ***поглавје во книга или монографија***
Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

Уплата за испечатен труд во списанието ММП изнесува 3.000, 00 денари и се уплаќаат на жиро сметката на: Македонско лекарско друштво
300000000211884 - Комерцијална банка
со цел на дознака : уплата за стручен труд

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Авторите што сакаат да објавуваат трудови во списанието треба да ја имаат уплатено членаринатa за тековната година во висина од 1440 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или преку телефон.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД - 3162 557.