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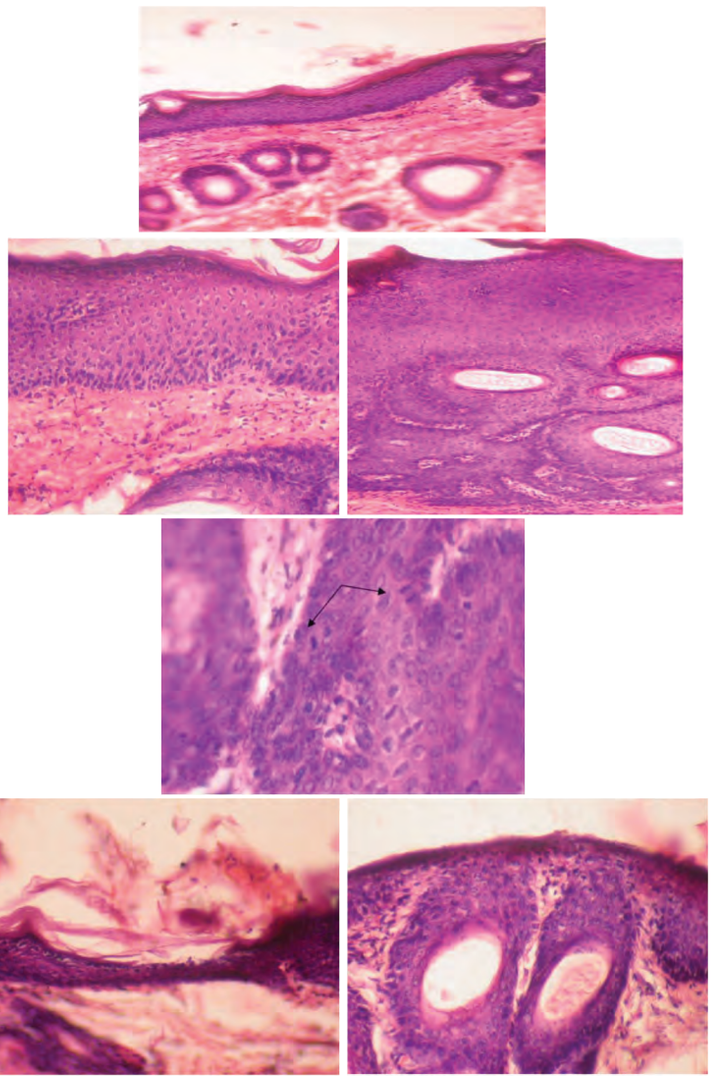
CONTENT HIGHLIGHTS:

CHARACTERISTICS OF MORPHOLOGICAL CHANGES IN THE SKIN OF PATIENTS WITH ALLERGODERMATOSES DURING LONG-TERM EXTERNAL APPLICATION OF FLUORINED STEROIDS

Yanina Kutasevych, Mykola Lyapunov, Iryna Ziuban, Iryna Mashtakova



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PREGABALIN RICHTER

O NOUĂ VIAȚĂ FĂRĂ DURERE

Capsule 75 mg N 56	Capsule 150 mg N 56	Capsule 300 mg N 56

- **Reduce durerea din ziua a 2 de tratament[1]**
- **Eficient în diverse tipuri de durere neuropată[1]**
- **Cea mai indicată pregabalină în Republica Moldova[2]**

Denumirea comercială a medicamentului: Pregabalin-Richter 75 mg, 150 mg, 300 mg capsule. **Compoziția calitativă** *și* **cantitativă:** fiecare capsulă conține pregabalină 75 mg, 150 mg, 300 mg respectiv.**Indicații terapeutice:** *Durere neuropată:* este indicat pentru tratamentul durerii neuropate periferice **și** centrale la adulți. *Epilepsie:* este indicat ca tratament adjuvant, la adulții cu convulsii parțiale, cu sau fără generalizare secundară. *Tulburare anxioasă generalizată:* este indicată pentru tratamentul tulburării anxioase generalizate (TAG) la adulți. **Doze și mod de administrare**: Doza variază între 150 și 600 mg pe zi administrată în 2 sau 3 prize. *Durere neuropată:* Tratamentul cu pregabalină poate fi inițiat cu o doză de 150 mg pe zi, administrată fracționat în două sau trei prize. În funcție de răspunsul individual **și** de tolerabilitatea pacientului, doza poate fi crescută la 300 mg pe zi după un interval de 3 până la 7 zile și, dacă este necesar, până la doza maximă de 600 mg pe zi, după încă un interval de 7 zile. *Epilepsie:* Tratamentul cu pregabalină poate fi inițiat cu o doză de 150 mg pe zi, administrată fracționat în două sau trei prize. În funcție de răspunsul individual și tolerabilitatea pacientului, doza poate fi crescută la 300 mg pe zi după o săptămână. Doza maximă de 600 mg pe zi poate fi atinsă după încă o săptămână. *Tulburare anxioasă generalizată:* Doza variază între 150 **și** 600 mg pe zi, administrată fracționat în 2 sau 3 prize. Necesitatea tratamentului trebuie reevaluată regulat. Tratamentul cu pregabalină trebuie inițiat cu 150 mg pe zi. În funcție de răspunsul individual și tolerabilitatea pacientului, doza poate fi crescută la 300 mg pe zi după un interval de o săptămână. După încă o săptămână, doza poate fi crescută la 450 mg pe zi. Doza maximă de 600 mg pe zi poate fi atinsă după încă o săptămână se poate.Dacă tratamentul trebuie întrerupt, se recomandă ca acest lucru să fie făcut treptat, timp de minim o săptămână, indiferent de indicație. *Insuficiență renală* Pregabalina se elimină din circulația sistemică în primul rând prin excreție renală, sub formă de medicament netransformat. Deoarece clearance-ul pregabalinei este direct proporțional cu clearance-ul creatininei, reducerea dozei la pacienții cu afectarea funcției renale trebuie individualizată în concordanță cu clearance-ul creatininei (CLcr). Nu este necesară ajustarea dozelor la pacienții cu *insuficiență hepatica. Copii și adolescenți* Siguranța și eficacitatea administrării Pregabalin - Richter la copii cu vârsta sub 12 ani și adolescenți (între 12 și 17 ani) nu au fost stabilite. *Vârstnici* Este necesară reducerea dozei de pragabalină din cauza scăderii funcției renale. *Mod de administrare* Poate fi administrat cu sau fără alimente. Numai pentru administrare orală. **Contraindicații:** Hipersensibilitate la substanța activă sau la oricare dintre excipienții. **Atenționări și precauții speciale pentru utilizare:** Pacienți cu diabet zaharat: pot necesita ajustarea medicamentelor hipoglicemiante. Reacții de hipersensibilitate: Dacă apar simptome de angioedem, tratamentul cu pregabalină trebuie întrerupt imediat. Amețeală, somnolență, pierderea conștienței, confuzie și afectare mentală: pacienții trebuie avertizați să fie prudenți până când se obișnuiesc cu posibilele reacții adverse ale medicamentului. Efecte asupra vederii: Întreruperea tratamentului cu pregabalină poate duce la dispariția sau reducerea acestor simptome vizuale. Insuficiență renală: Au fost raportate cazuri de insuficiență renală iar întreruperea tratamentului cu pregabalină, **în** câteva cazuri, a demonstrat reversibilitatea acestei reacții adverse. Nu sunt disponibile date suficiente privind întreruperea tratamentului cu medicamente antiepileptice administrate concomitent atunci când s-a realizat controlul convulsiilor cu pregabalină, și care să susțină monoterapia cu pregabalină. După întreruperea tratamentului de lungă sau scurtă durată,la unii pacienți s-au observat simptome de întrerupere. Au existat raportări de insuficiență cardiacă congestivă la anumiți pacienți cărora li s-a administrat pregabalină. Pregabalina trebuie utilizat cu precauție la acești pacienți. Reacția adversă poate să dispară la **întreruperea** tratamentului cu pregabalină. **Reacții adverse:** Înt-un program clinic (peste 8900 pacienți) cele mai frecvente reacții adverse raportate au fost amețeală și somnolență. Reacțiile adverse au fost, de obicei, de intensitate ușoară până la moderată. Reacțiile adverse prezentate pot fi asociate *și* cu bolile preexistente *și*/sau cu medicamentele administrate concomitent. *În* lista de mai jos, sunt incluse reacții adverse adiționale raportate după punerea pe piață:foarte frecvente-amețeală,somnolență,cefalee; frecvente- rinofaringită,neutropenie,apetit alimentar crescut,stare de euforie, confuzie,iritabilitate,dezorientare,insomnie,libido scăzut,ataxie,tulburări de coordonare,tremor,dizartrie,amnezie,tulburări de atenție,-parestezii,hipoestezii,sedare,tulburări de echilibru,letargie,vedere încețoșată,diplopie,vertij,vărsături,greață,constipație,diaree,flatulență,distensie abdominală,xerostomie,crampe musculare,artralgii,dureri lombare,dureri la nivelul membrelor,spasm cervical,disfuncție erectile,edeme peiferice,edeme,mers anormal,căzături,senzație de ebrietate,stare de rău,fatigabilitate,creștere a greutății corporale. **Data și numărul autorizației:** 75 mg -26071;150 mg- 26072; 300 mg-26073 din 06.03.2020**. 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Referințe:

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RESEARCH ARTICLE

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Hybrid vascular approach reduces the length of hospital stay in patients with chronically threatening limb ischemia and multilevel atherosclerotic lesions

Sorin Barat

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ABSTRACT

Introduction. Chronic limb-threatening ischemia represents the advanced stage of atherosclerosis and is often associated with significant cardiovascular morbidity, resulting in high mortality rates. The hybrid approach combines surgical and endovascular techniques, allowing for optimal revascularization of multilevel lower limb atherosclerotic lesions. Additionally, the hybrid approach offers the advantages of shorter procedure times and reduced trauma compared to the classical method. It is also expected to result in a shorter length of hospital stay for patients. Therefore, the aim of this study is to analyze the relationship between the hybrid approach and the length of hospital stay compared to the classical vascular surgical approach in patients with chronic limb-threatening ischemia, multilevel atherosclerosis, and a high anesthesiologic risk.

Material and methods. The study compares the total and postoperative lengths of stay between two groups: a prospective group (N = 48) of patients treated with hybrid revascularizations, and a control group (N = 50) treated with classical vascular revascularizations. The included patients in both groups had multilevel atherosclerotic lesions (including aorto-iliac, femuro-popliteal, and runoff) and chronic limb-threatening ischemia (Fontaine grade III and IV).

Results. The study analyzed the total and postoperative lengths of stay in both groups, including ischemia-based subgroups. The results showed that both the total and postoperative lengths of stay were significantly shorter in the hybrid approach group compared to the control group.

Conclusions. In cases where hybrid revascularizations were used, the length of hospital stay for patients with chronic limb-threatening ischemia and multilevel atherosclerosis is significantly shorter compared to the classical vascular surgical method.

Key words: multilevel atherosclerotic lesions, chronic limb-threatening ischemia, hybrid revascularizations, length of stay..

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Until now, there has been a dearth of objective data comparing the length of hospital stay between patients treated with hybrid revascularizations for chronic limb-threatening ischemia and multilevel atherosclerotic lesions, and those treated using the classical method of surgical revascularization.

The research hypothesis

Patients treated with hybrid revascularizations for chronic limb-threatening ischemia and multilevel atherosclerotic lesions experience a shorter length of hospital stay compared to those treated using the classical method of surgical revascularization.

The novelty added by manuscript to the already published scientific literature

Endovascular surgery is a relatively new specialty in the Republic of Moldova, while hybrid revascularization itself represents a novel treatment approach for patients with multilevel atherosclerotic lesions. Therefore, conducting an analysis of the length of hospital stay for patients undergoing hybrid revascularizations compared to classical surgical revascularizations would contribute valuable data to the existing literature.

Introduction

In 2010, estimates suggested that over 200 million people worldwide were living with PAD. This represented a 23.5% increase since 2000, which is largely attributed to aging populations and the growing prevalence of risk factors, particularly diabetes mellitus [1]. While CLTI is widely recognized as a significant global healthcare issue, reliable epidemiological data on CLTI are scarce [1]. CLTI likely accounts for less than 10% of all PAD cases, and individuals undergoing amputation due to CLTI face a significantly higher risk of premature death [1]. Without treatment, the risk of lower limb loss in CLTI patients is approximately 25% within one year [2]. CLTI represents the advanced stage of atherosclerosis and is often accompanied by significant cardiovascular morbidity, resulting in high mortality rates due to stroke and myocardial infarction [2]. Without timely identification of risk factors and effective management of comorbidities, the prognosis for CLTI patients is generally unfavorable, with a mortality rate ranging from 20% to 26% within one year of diagnosis [2, 3]. A study conducted on 574 CLTI patients who did not undergo limb revascularizations revealed that 31.6% of patients died from cardiovascular causes, while 23% required major amputations [2, 4]. Hence, the objective of this study is to analyze the impact of hybrid revascularizations on the length of hospital stay for patients with CLTI, multilevel atherosclerosis, and a high anesthesiological risk.

Materials and methods

This study utilized a prospective, superiority design, comprising a study group (N = 48) and a historical control group (N = 50) from the period of 2010-2015. The primary objective of the study was to compare the efficacy of the hybrid vascular approach with the classical vascular surgical treatment for patients with multilevel atherosclerosis and CLTI. The ultimate endpoint of the study was to assess the impact of the hybrid approach on reducing morbidity and mortality within the study group. The sample size for the study group was determined using the "Mureșanu formula." The study was conducted at the Republican Clinical Hospital, while the control group was formed by selecting every 5th patient file from the anonymized and codified records of 250 patients in the hospital archive from the 2010-2015 period. Inclusion criteria for the study were as follows: (1) men and women aged over 50 years old; (2) presence of multilevel atherosclerotic lesions; (3) diagnosis of CLTI based on Fontaine grades III and IV or Rutherford 4-6 classification. Exclusion criteria for the study were: (1) presence of an aortic infrarenal aneurysm greater than 5.5cm; (2) inoperable patients; (3) patients in terminal stages; (4) allergic to iodinated contrast material; (5) presence of isolated atherosclerotic lesions; (6) absence of CLTI; (7) refusal to sign the informed consent; (8) non-compliant patients.

The study group consisted of all consecutive patients meeting the inclusion criteria, with a total of N = 50. These patients underwent hybrid interventions, which involved a combination of one open surgical reconstruction and another endovascular procedure. Two patients were excluded from the analysis due to their failure to attend the follow-up visits. The follow-up assessments were conducted at one month and three months post-treatment. Additionally, two subgroups were formed based on the severity of ischemia, categorized as Fontaine grade III and IV. The study analyzed both the total length of hospital stay and the postoperative length of hospital stay for the patients. A database was created to store the collected data, which was subsequently subjected to statistical analysis using the "SPSS" software. The statistical tests employed in the analysis included chi-square, p-value calculations, and frequency analysis. The study obtained ethical approval from the Ethics Committee on 14.11.2016, with reference number 17.

Results

Demographic data analysis revealed an equal distribution between men and women in the study population, with no significant statistical difference observed ($\chi2 = 0.004$, df = 1, p = 0.952). In both the study group and the control group, the majority of patients were men: 44 patients (91.7%; 95% CI [84.0-98.0]) in the study group and 46 patients (92.0%; 95% CI [84.0-98.0]) in the control group. The most common age group among the patients was 60-69 years, comprising 21 patients (43.8%; 95% CI [29.4-57.8]) in the study group and 28 patients (56.0%; 95% CI [40.1-70.0]) in the control group. The next most prevalent age group was 50-59 years, with 17 patients (35.4%; 95% CI [22.2-50.0]) in the study group and 13 patients (26.0%; 95% CI [14.0-38.0]) in the control group. However, the data did not reveal any significant statistical difference between the two groups in terms of age distribution ($\chi2 = 1.979$, df = 3, p = 0.577).

The most prevalent comorbidity among the patients was arterial hypertension, with a higher rate observed in the study group (44 patients; 91.7%; 95% CI [83.3-98.1]) compared to the control group (36 patients; 72.0%; 95% CI [59.1-85.1]). This difference between the two groups was statistically significant ($\chi2 = 6.317$, df = 1, p = 0.012). Ischemic heart disease was the second most frequent comorbidity, with similar rates observed in both the study group (30 patients; 62.5%; 95% CI [49.0-77.8]) and the control group (32 patients; 64.0%; 95% CI [51.0-77.8]), showing no

significant statistical difference (χ2 = 0.024, df = 1, p = 0.878). Chronic obstructive pulmonary disease was the third most common comorbidity, being more prevalent in the control group (32 patients; 64.0%; 95% CI [51.0-77.8]) compared to the study group (23 patients; 47.9%; 95% CI [32.6-62.7]), but this difference did not reach statistical significance (χ2 = 2.573, df = 1, p = 0.109). Cerebrovascular disease, the fourth comorbidity analyzed, was identified at similar rates in both the study group and the control group. In the study group, 20 patients (41.7%; 95% CI [27.7-56.5]) had cerebrovascular disease, while in the control group, 16 patients (32.0%; 95% CI [19.6-44.7]) had the same condition. However, there was no significant statistical difference between the two groups (χ2 = 0.985, df = 1, p = 0.321). The prevalence of DM was relatively equal in both groups. In the study group, 17 patients (35.4%; 95% CI [21.2-50.0]) had DM, while in the control group, 13 patients (26.0%; 95% CI [13.7-37.5]) had DM. The statistical analysis showed no significant difference between the two groups (χ2 = 1.022, df = 1, p = 0.312). The majority of patients in both the study group (42 patients; 87.5%; 95% CI [76.5-95.9]) and the control group (41 patients; 82.0%; 95% CI [72.0-92.0]) had an anesthesiological risk score of ASA 3 (Severe systemic disease that is not incapacitating, mortality 1.8%) based on the ASA grading scale. However, there was no significant statistical difference observed between the groups (χ2 = 0.571, df = 1, p = 0.450).

Analyzing the total length of hospital stay in the two groups in relation to the grade of limb ischemia, it was found that the highest frequency for Fontaine grade III consisted of lengths of stay within the period of 9-12 days. Out of 32 cases in the study group, 11 cases fell within this period, compared to the control group where the period with the highest frequency was more than 14 days. Out of 22 cases in the control group, 11 cases had a length of hospital stay exceeding 14 days (Table 1). Thus, there was a significant statistical difference between the groups (χ2 = 10.53; df = 4; p = 0.03). Furthermore, a moderately significant statistical difference was observed (χ2 = 15.53; df = 4; p = 0.004; V. Cramer = 0.536).

Table 1. Overall length of hospital stay in groups for Fontaine grade III limb ischemia.

Length of hospital stay periods	Study group (N = 32)	Control group (N = 22)	p
3-5 days	3	–	
6-8 days	8	–	$\chi^2 = 15.53$
9-11 days	11	4	df = 4
12-14 days	5	7	p = 0.004
> 14 days	5	11	

Note: p – significance level; χ^2 – Pearson test; df – degrees of freedom.

Regarding the length of hospital stay after the intervention, it was found that patients with Fontaine grade III limb ischemia from the study group required a period of 3-5 days in 17 out of 32 cases. In contrast, patients from the control group required 6-8 days in 7 out of 22 cases and 9-11 days in 7 out of 22 cases (Table 2). A moderately significant statistical difference was observed between the groups (χ2 = 12.73; df = 4; p = 0.013; V. Cramer = 0.486).

Table 2. Postoperative length of hospital stay in groups for Fontaine grade III limb ischemia.

Length of hospital stay periods	Study group (N = 32)	Control group (N = 22)	p
3-5 days	17	4	
6-8 days	12	7	$\chi^2 = 12.73$
9-11 days	2	7	df = 4
12-14 days	1	3	p = 0.013
> 14 days	–	1	

Note: p – significance level; χ^2 – Pearson test; df – degrees of freedom.

When comparing the length of hospital stay of patients with Fontaine grade IV limb ischemia, it was discovered that the study group had the highest frequency for the period of 6-8 days, with 5 out of 16 cases falling within this range. Conversely, in the control group, the majority of patients required more than 14 days, specifically 18 out of 28 cases (Table 3). This difference between the groups was found to be statistically significant with a moderate level of significance (χ2 = 10.93; df = 4; p = 0.027; V. Cramer = 0.498).

Table 3. Overall length of hospital stay in groups for Fontaine grade IV limb ischemia.

Length of hospital stay periods	Study group (N = 16)	Control group (N = 28)	p
3-5 days	1	–	
6-8 days	5	1	$\chi^2 = 10.93$
9-11 days	2	2	df = 4
12-14 days	4	7	p = 0.027
> 14 days	4	18	

Note: p – significance level; χ^2 – Pearson test; df – degrees of freedom.

Regarding the postoperative length of hospital stay in patients with Fontaine grade IV limb ischemia, a significant statistical difference was observed between the study and control groups (χ2 = 10.53; df = 4; p = 0.032; V. Cramer = 0.489). Among patients with Fontaine grade IV limb ischemia, the highest frequency was found in the 3-5 day period, with 6 out of 16 cases in the study group. In the control group, the majority of cases were in the 9-11 day period, with 10 out of 28 cases (Table 4).

Table 4. Postoperative length of hospital stay in groups for Fontaine grade IV limb ischemia.

Length of hospital stay periods	Study group (N = 16)	Control group (N = 28)	p
3-5 days	6	1	
6-8 days	5	7	$\chi^2 = 10.53$
9-11 days	2	10	df = 4
12-14 days	2	7	p = 0.032
> 14 days	1	3	

Note: p – significance level; χ^2 – Pearson test; df – degrees of freedom.

Discussions

Hybrid interventions have become an integral part of the strategy for limb salvage in patients with multilevel arterial occlusive disease. Technical success, early results, as well as long-term results, have shown to be at least comparable to conventional endovascular and open vascular procedures.

Hybrid revascularization offers the efficiency and convenience of a single-stage revascularization [5]. Currently, most of the combined procedures are performed by vascular surgeons trained in both open and endovascular surgery. Simultaneous hybrid interventions are associated with potential benefits such as decreasing the length of stay, the absence of the need to delay complete revascularization of the ischemic limb, avoidance of puncture site complications due to direct surgical access, and the possibility of open surgical correction of inadequate endovascular revascularization sites [6, 7]. In a study by Peter L. Faries et al., all the combined interventions were performed in a staged manner, with an interval of 3.1 days between the open and endovascular stages. When comparing simultaneous and staged hybrid procedures, factors such as patient comfort and convenience, length of stay, procedure costs, and the possibility of staging the procedure were taken into consideration. These factors demonstrate the advantages of choosing the simultaneous hybrid procedure over the staged approach [8]. Elbadawy A. et al., in their study, recommend decision-making based on the patient's risk and the severity of limb ischemia when determining the appropriate strategy [9]. In a review conducted by Christos D. Liapis and Elias A. Tzortzis, it was concluded that combining open vascular and endovascular techniques yields greater benefits compared to using each technique alone [10]. James L. Ebaugh et al., in their study, identified 5 variables as confounders in the relationship between staged and same-day procedures. Patients with the following conditions were excluded from the final subgroup analysis: (1) gangrene; (2) ischemic rest pain; (3) non-elective admission; (4) chronic heart failure; and (5) renal failure. After excluding patients with these confounders, hospital charges and length of hospital stay were compared once again. The results indicate that when performing elective hybrid procedures in patients without gangrene, ischemic rest pain, chronic heart failure, or renal failure, conducting both the endovascular and open portions on the same day significantly reduces total hospital charges by 78% and length of hospital stay by 133% [11]. Therefore, compared to the staged hybrid procedure, the simultaneous procedure may lead to a shorter length of stay, reduced procedural costs, and a broader range of revascularization options by combining open and endovascular techniques [12, 13, 14].

Conclusions

The length of hospital stay for patients with CLTI and multilevel atherosclerotic lesions is significantly reduced when hybrid revascularizations are used compared to conventional revascularizations.

Abbreviations

CLTI – chronic limb-threatening ischemia; PAD – peripheral arterial disease; DM – diabetes mellitus.

Ethics approval

This study was approved by the Research Ethics Committee (the name of the ethics committee or institutional review board) (Reference No 17 from 14 November 2016).

Declaration of conflict of interests

Nothing to declare.

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RESEARCH ARTICLE

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Computed tomography findings of abdominal textiloma

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ABSTRACT

Background. The unintentional leaving of gauze sponges in the abdomen after laparotomy is a rare but serious medical error. The diagnosis of a textile foreign body can be challenging due to its rarity, potential long-term asymptomatic evolution, and nonspecific imaging findings that may be unfamiliar to radiologists.

Materials and methods. The data of 13 radiologically identified and surgically confirmed cases of abdominal textilomas treated over a 15-year period were assessed retrospectively. There were 10 women (76.9%) and 3 men (23.1%); the average age was 38.5±4.7 years. The average interval between the previous procedure and the diagnosis of textiloma was 25.3±15.2 months, ranging from 1 day to 16 years.

Results. The most common imaging patterns seen on CT included masses with a typical spongiform structure with numerous small air bubbles and surrounded by a thin capsule, as well as a high-density, well-circumscribed lesion, sometimes with mottled calcification, and a dense capsule with intense contrast accumulation. Based on surgical history, physical examination, and CT scan findings, a likely diagnosis of textiloma was made before surgery in 11 (84.6%). In all patients, a repeated open surgery was necessary to remove textile foreign bodies.

Conclusions. The possibility of an abdominal textiloma should be considered in the differential diagnosis of any postoperative patient who presents with pain, infection, or a palpable mass. CT scanning is a practical and highly sensitive diagnostic tool for detecting textilomas with characteristic imaging features in both chronic encapsulated and acute inflammatory manifestations.

Keywords: foreign bodies, surgical sponge, textiloma, computed tomography, radiological findings, repeated surgery.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

A textile foreign body inadvertently left in the abdominal cavity is a rare and severe iatrogenic complication. The diagnosis of textiloma is often difficult due to possible long-term previous asymptomatic evolution as well as nonspecific and poorly familiar to physicians imaging findings.

The research hypothesis

CT is a practical, useful, and highly sensitive diagnostic tool for identifying abdominal textilomas with characteristic imaging findings in both chronic encapsulated and acute inflammatory manifestations.

The novelty added by manuscript to the already published scientific literature

The possibility of an abdominal textiloma should be considered in the differential diagnosis of any postoperative patient with pain, infection, or a palpable mass. CT scans serve as a decisive imaging method for the diagnosis of textiloma, its exact anatomical location, the presence of possible complications, and justifying the need for repeated surgery.

Introduction

Textiloma denotes a cotton foreign body or textile matrix remaining inside the patient's body after the end of a surgical procedure. Most commonly, they are diagnosed in the abdominal cavity [1, 2]. The unintentional leaving of gauze sponges in the abdomen following a laparotomy is a rare but serious medical error. Depending on its location and evolution, the remaining foreign body can either undergo aseptic encapsulation, which leads to pseudotumor appearance, or cause a local acute inflammatory response with abscess development [3, 4]. The time interval before detection of textiloma can vary from the immediate postoperative period to decades after surgery. The diagnosis of a textile foreign body is often difficult due to the rarity of the condition, which is usually unexpected by clinicians, possible long-term previous asymptomatic evolution, and nonspecific and imaging findings that are poorly familiar to radiologists [3, 5].

Materials and methods

The present study was conducted in two medical institutions: The Institute of Emergency Medicine and *Gheorghe Paladi* Municipal Clinical Hospital No.1. This study was approved by the Research Ethics Committee of the *Nicolae Testemiţanu* State University of Medicine and Pharmacy, protocol No.48, from February 12, 2020. Data from computed tomography (CT) identified and surgically confirmed cases of abdominal textilomas treated over a 15-year period (2006–2020) were analyzed retrospectively using interviews with surgeons who were willing to disclose those cases of foreign body retention. In some patients, CT scans were performed in private medical centers ("Excellence", "Magnific", and the German Diagnostic Center). The study recorded several factors related to patients diagnosed with textiloma, including their demographics, previous surgeries, clinical manifestations, preliminary diagnosis, and examination tools used. The study also looked at the interval between the causal procedure and textiloma diagnosis, the type of surgical intervention, the location of the foreign body, and the disease's further evolution.

The study emphasized cases with detailed CT images, which were reconstructed in 3D using thin sections (1 mm) in coronal and sagittal planes to provide a better understanding of the lesion's extent and involvement of adjacent structures. While the data and results of X-rays and abdominal ultrasonography (US) were also considered, the study focused on the clinical significance of CT images.

Thirteen cases of abdominal textiloma were included in our study. Table 1 provides a summary of the patients' characteristics, which showed that 10 of the patients were women (76.9%) and 3 were men (23.1%). The average age of the patients was 38.5±4.7 years, with a range of 20 to 74 years.

Of the 13 cases, 7 patients (53.8%) underwent a primary surgical procedure due to general surgical conditions, while 6 patients (46.1%) underwent obstetric or gynecological surgeries. The average interval between the previous procedure and the diagnosis of textiloma using CT was 25.3±15.2 months, ranging from 1 day to 16 years.

Case 1. A 29-year-old woman underwent a caesarean section. She returned 3 weeks later with abdominal pain and a clearly palpable mass in the right part of the abdomen. On the native CT scan, a well-defined hyperdense mass measuring 85x70x65 mm was revealed in the mesogastric area, slightly to the right of midline, with numerous small gaseous inclusions (Figure 1). A repeat open surgery was performed with the simple retrieval of a textiloma (gauze sponge). There was no involvement of the surrounding organs. Postoperative evolution was favorable.

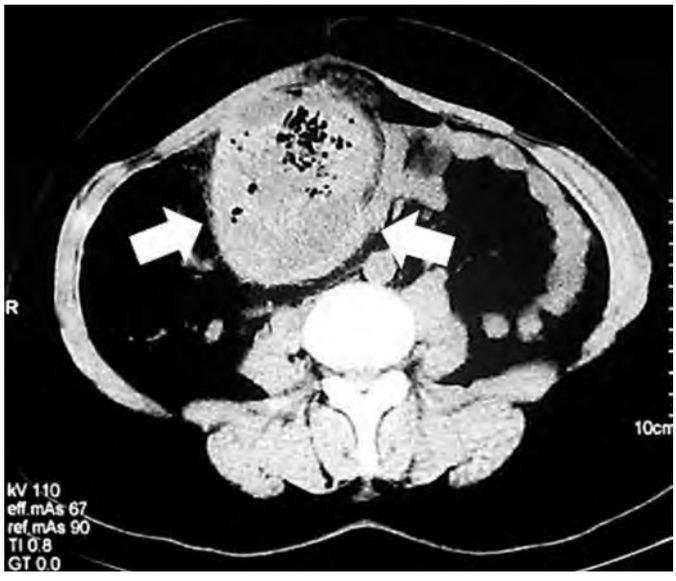

Fig. 1. Case 1: A native axial abdominal CT scan shows a well-defined hyperdense mass in the mesogastric area, slightly to the right from midline, with numerous small gas inclusions (arrows).

Case 2. A 28-year-old female patient had an incisional abdominal hernia after a lower median laparotomy. Somewhere around 5 months after hernia repair with a synthetic mesh, she developed vague abdominal pain, anorexia, and constipation. In prehospital conditions, US and multidetec-

Table 1. Clinical and radiological characteristics of patients with abdominal textiloma.

No.	Sex, age (years)	Previous surgery	Interval from surgery	Preliminary diagnosis	Location and size of the textiloma on CT
1	F, 29	Cesarean section	24 days	Infected hematoma	Right mesogastric area; 85x70x65 mm*
2	F, 28	Incisional hernia repair	5 months	Abdominal mass (textiloma)	Midline pelvis; 37x43x60 mm
3	M, 52	Inguinal hernia repair	5,5 years	Retroperitoneal cyst	Right iliac area; 40x35x35 mm
4	F, 27	Drainage of postpartum parametrial hematoma	5 days	Interintestinal hematoma (textiloma)	Left mesogastric area; 88x108x120 mm
5	F, 26	Ruptured ectopic pregnancy	2 months	Abdominal abscess	Left iliac area; 85x115x95 mm
6	F, 32	Ruptured ectopic pregnancy	6 months	Abdominal abscess (textiloma)	Right subhepatic space; 72x98x74 mm
7	F, 24	Left hemicolectomy	2,5 months	Intestinal obstruction	Right mesogastric area; 35x36x68 mm†
8	F, 20	Spleno-renal shunt	16 years	Ovarian dermoid cyst	Left iliac area; 50x46x52 mm
9	F, 74	Oversewing of the bleeding duodenal ulcer	3 months	Chronic purulent fistula (textiloma)	Right mesogastric area; 58x69x95 mm
10	F, 26	Cesarean section	1 day	Foreign body (textiloma)	Right hypogastric area; 40x73x124 mm
11	F, 45	Total hysterectomy	4 years	Abdominal mass (textiloma)	Left pelvis; 43x65x50 mm
12	M, 57	Distal partial gastrectomy	16 days	Subhepatic abscess (textiloma)	Midline epigastrium; 60x117x51 mm
13	M, 60	Hartmann's procedure	16 days	Abdominal abscess (textiloma)	Left subphrenic space; 109x85x125 mm

Note: * – the textiloma sizes are presented in the following order: anteroposterior x lateral x vertical; † – the only case of complete intraluminal migration of textiloma and its localization inside the jejunal loop.

tor contrast CT scans were sequentially performed. On the latter, in the pelvis almost along the midline, a rounded, encapsulated mass measuring 37x43x60 mm with a few air bubbles inside is visualized. The capsule is dense, reaches a thickness of 4 mm, and showed significant enhancement on post-contrast study (Figure 2). Abdominal textiloma was suspected, and the patient was admitted for redo surgery. The foreign body (gauze sponge) was removed via laparotomy. An uncomplicated recovery followed. No pathological clinical events were noted during the patient's 1-year follow-up.

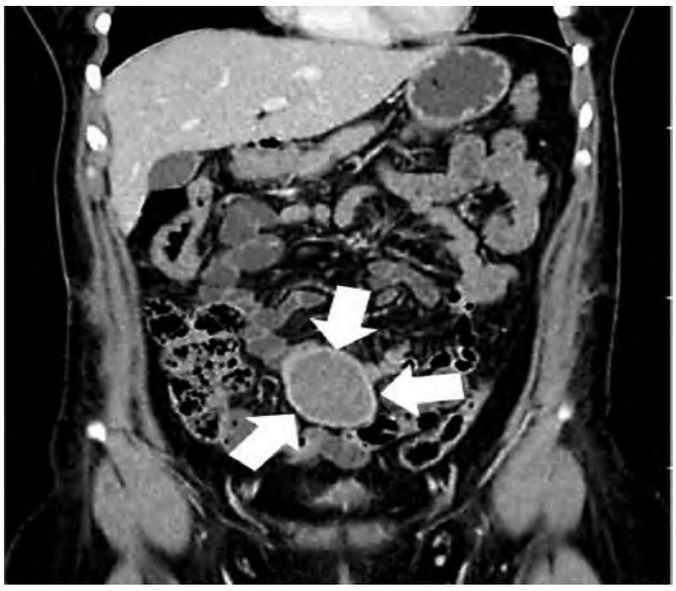

Fig. 2. Case 2: A post-contrast coronal CT scan revealed a rounded, encapsulated mass in the pelvis, almost in the midline. Note the dense capsule with enhancement on the post-contrast study (arrows).

Case 3. A 52-year-old man underwent inguinal hernia repair using local tissues. After the surgery, the patient remained asymptomatic without any complaints. However, during a follow-up ultrasound examination 5.5 years later, a cystic abdominal mass was discovered. A CT scan was recommended, revealing a well-defined, rounded formation measuring 40x35x35 mm in size with inhomogeneous density in the right iliac area. The patient underwent an elective open surgery, during which an elastic mass, unrelated to surrounding organs, was removed. Upon gross pathological examination of the specimen, a non-degraded gauze swab was found. The patient's postoperative period was uneventful.

Case 4. A 27-year-old woman who underwent a physiological delivery experienced a ruptured cervix, vaginal and parametric hematomas, and intra-abdominal bleeding. A median laparotomy was performed on the following day to address the hematoma and ensure hemostasis. The patient experienced severe abdominal pain, bloating, lack of peristalsis, and signs of intra-abdominal infection during the early postoperative period. Plain radiography and repeated transabdominal ultrasounds were inconclusive. Five days after the primary surgery, a CT scan was conducted, revealing a heterogeneous mass with air bubbles and encysted liquid measuring 88x108x120 mm in the left mesogastric area. Subsequent relaparotomy uncovered a textiloma (a large surgical gauze pad) that was removed. The postoperative course was normal, with wound healing achieved through primary intention.

Case 5. A 26-year-old woman underwent surgery for an ectopic pregnancy with intra-abdominal bleeding and a subsequent tubectomy. Two months later, she was urgently admitted to the surgical department with severe pain in the left iliac fossa, asthenia, and fever. A painful, elastic mass was palpated in the left lower abdomen. An abdominal CT revealed a well-defined oval structure measuring 85x115x95 mm with predominantly air content in the left iliac region, covered with a dense capsule up to 10-15 mm thick. The

patient underwent relaparotomy with suspicion of a late postoperative abscess. A foreign body (gauze sponge) was found inside the cavity formed by the omentum and sigmoid colon. The textiloma was removed, and the infected cavity was debrided and drained. However, a large bowel fistula appeared during the postoperative period. Although the fistula eventually closed spontaneously following conservative treatment, the patient's hospital stays lasted 46 days.

Case 6. A 32-year-old woman presented with sudden and progressively worsening abdominal pain and impaired intestinal passage six months after undergoing a midline laparotomy and tubectomy for an ectopic pregnancy. Despite receiving conservative treatment, the patient's symptoms did not improve, and she sought urgent care at the surgical department. Upon physical examination, her abdomen was swollen, diffuse tender and resistant. Ultrasound imaging showed an isoechoic lesion in the upper right abdomen with an incomplete hyperechoic peripheral wall. An emergent CT scan revealed a 72x98x74 mm encapsulated mass with a cellular pattern and gas bubbles in the right subhepatic space. The mass was also compressing the ascending colon, and the radiologist suspected the presence of an intestinal fistula (as shown in Figure 3). During an emergency relaparotomy, surgeons discovered a foreign object – a gauze sponge soaked in intestinal contents – within the abdominal cavity, causing erosion of the bowel wall. The defect in the ascending colon was primarily closed, and the patient experienced an uneventful postoperative recovery. She was discharged after 15 days.

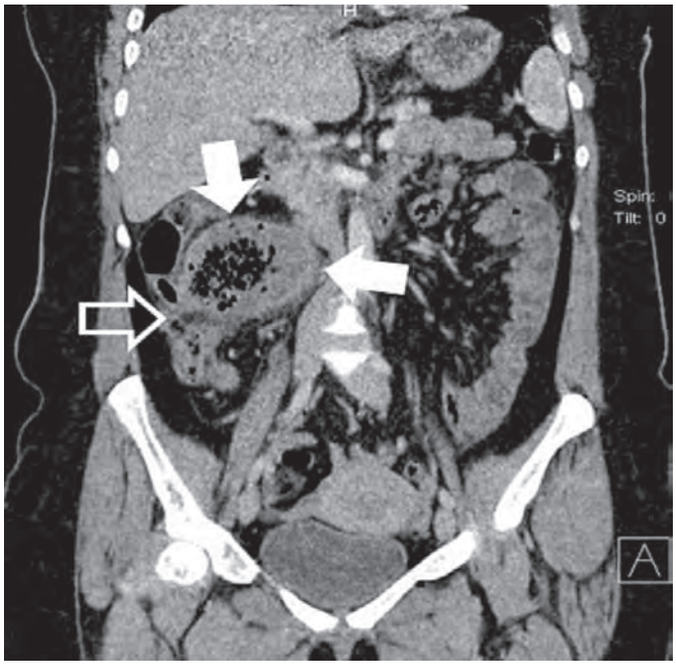

Fig. 3. Case 6: On contrast-enhanced coronal CT imaging, an encapsulated mass with a spongy appearance and gas bubbles is visible in the right subhepatic space (as indicated by the arrows). Note the compression of the ascending colon by mass and suspicion of intestinal fistula (open arrow).

Case 7. A 24-year-old woman was urgently admitted to the surgical department with intermittent diffuse abdominal pain, nausea, and repeated vomiting. Physical examination revealed moderate abdominal distension but no tenderness or peritoneal irritation. Two and a half months before she underwent a left-sided colectomy for dolichocolon and chronic constipation syndrome. Abdominal CT with intraluminal contrast revealed a marked distention of the proximal jejunal loops, as well as a blindly terminating loop of the small bowel within the right mesogastric area with a diameter of up to 5 cm, containing a mass measuring 35x36x68 mm in size with mixed liquid and air bubble contents, surrounded by heterogeneous high-density walls (up to +200 Hounsfield units) (Figure 4). The radiologist identified the mass as an accumulation of barium caused by an incomplete intestinal obstruction. The patient underwent surgery with suspicion of adhesive intestinal obstruction. During laparotomy, numerous dense adhesions were observed between the dilated jejunal loop and anterior abdominal wall, located about 100 cm from the Treitz ligament. While separating the adhesions, the foreign body (a crumpled surgical sponge) was found and removed from the lumen, which had caused the obstruction. After partially resecting the damaged segment, intestinal continuity was restored by an end-to-end anastomosis. The postoperative period was complicated by a deep surgical site infection and a subcutaneous evisceration. The patient stayed in the hospital for 30 days.

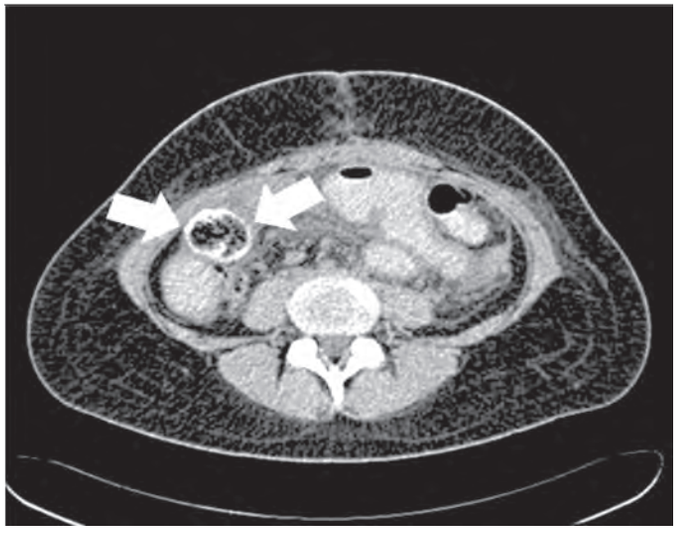

Fig. 4. Case 7: An axial abdominal CT scan with intraluminal contrast revealed a markedly dilated jejunal loop that was blindly terminating within the right mesogastric region. The loop contained an obscure mass with mixed fluid-bubble contents and was surrounded by high-density walls (arrows).

Case 8. A 20-year-old woman was electively admitted to the hospital. Sixteen years ago, at the age of 4, she underwent spleno-renal shunting for prehepatic portal hypertension and bleeding from dilated esophageal varices. An

outpatient CT scan with intraluminal contrast revealed a spherical mass in the left iliac region measuring 50x46x46 mm with well-defined contours and high soft tissue density (+46 Hounsfield units), but with hypodense areas (+16 Hounsfield units) and multiple mottled calcifications (Figure 5). The patient was asymptomatic. During laparotomy, a round, tumor-like mass of densely elastic consistency that closely adhered to the small intestine loop was found. The mass was removed without damaging the surrounding organs. A gauze pad was found inside the pseudotumor on gross specimen cutting. The postoperative period was uncomplicated.

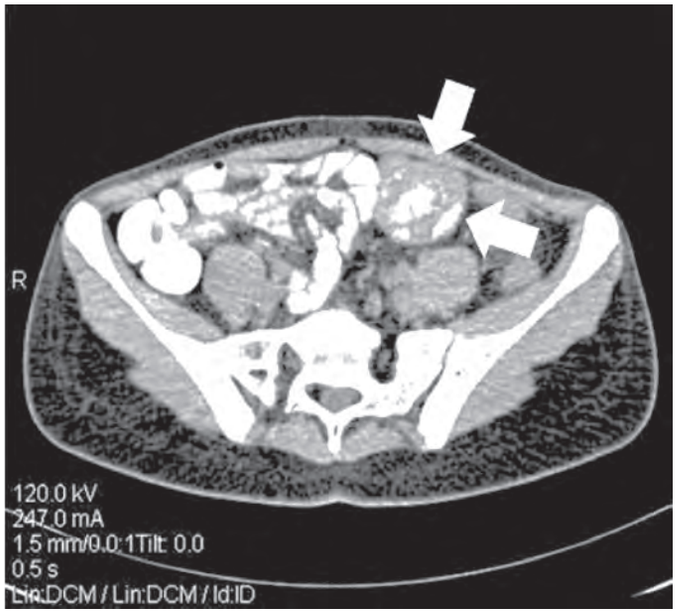

Fig. 5. Case 8: An axial abdominal CT scan with intraluminal contrast reveals a spherical mass in the left iliac area with well-defined contours, high soft tissue density, and multiple mottled calcifications (arrows).

and severe abdominal pain, there was suspicion of intra-abdominal bleeding from spontaneous rupture of the spleen. Abdominal ultrasound and CT scans were performed sequentially. On the CT scan, an irregular-shaped mass, relatively hyperdense, with numerous air bubbles, well delimited from surrounding tissues, measuring 40x73x124 mm was identified in the right mesogastric region (see Figure 6). The radiologist described the findings as a residual textile foreign body in the abdominal cavity, likely a retained surgical sponge. An urgent laparotomy was performed, and the gauze sponge was retrieved. The postoperative period was uneventful.

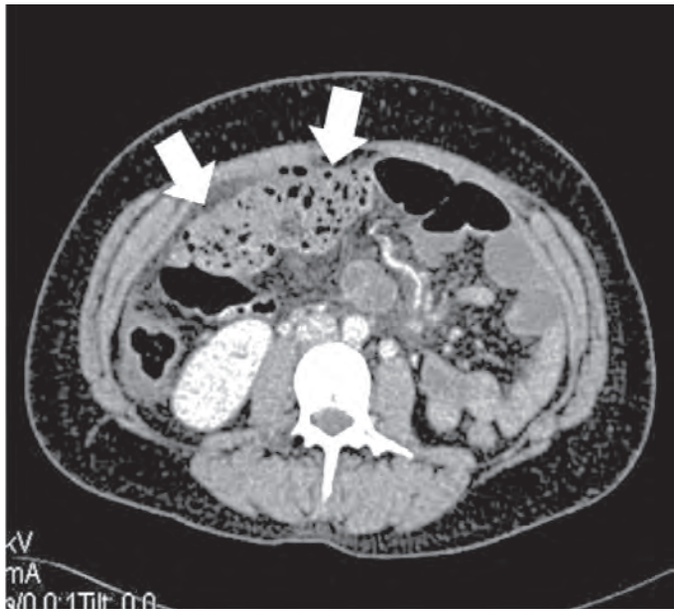

Fig. 6. Case 10: A post-contrast axial abdominal CT scan showed an irregular-shaped mass, well delimited, relatively hyperdense, with numerous air bubbles, located in the right mesogastric region (arrows).

Case 9. A 74-year-old woman underwent duodenotomy and hemostatic oversewing of a duodenal ulcer due to recurrent bleeding. In the postoperative period, a chronic purulent fistula opened in the scar after midline laparotomy, without any tendency to close over the next 3 months. An X-ray contrast study of the fistulous canal revealed a large intra-abdominal cavity with amorphous content. On CT, an inhomogeneous, oval-shaped mass measuring 58x69x95 mm with multiple gas inclusions was visualized in the right mesogastric area, surrounded by a capsule up to 6 mm thick. A diagnosis of a retained surgical sponge (textiloma) was made, which was confirmed during a subsequent laparotomy where the gauze sponge was removed. The postoperative course was uneventful.

Case 10. A 26-year-old woman at 28-29 weeks of pregnancy was urgently hospitalized for premature detachment of the placenta, and an emergency cesarean section was performed. The next day, due to the patient's poor condition

Case 11. A 45-year-old woman who underwent total hysterectomy 4 years ago presented with moderate abdominal pain. Physical examination revealed a palpable mass in the left suprapubic area. A CT scan of the pelvis revealed a solid mass measuring 43 x 65 x 50 mm with a high density capsule enhancement in the post-contrast phase located to the left of midline. The diagnosis of textiloma (surgical gauze sponge) was made, and elective surgery was performed to remove the mass along with a fragment of a covering omentum. The postoperative period was uneventful.

Case 12. A 57-year-old man had a long-standing duodenal ulcer and presented with marked gastric outlet stenosis. In the early postoperative period following a Billroth-I distal partial gastrectomy, the patient developed progressive signs of abdominal infection: tenderness in the upper abdomen, muscular resistance, peritoneal signs, high fever, and leukocytosis. Abdominal ultrasound showed a well-defined multiseptated fluid collection measuring 75x32x70 mm. CT

scan with intravenous contrast revealed a typical "spongiform" structure of 60x117x51 mm, with areas of fluid and entrapped small gas bubbles, located in the epigastrium, in the projection of the omental bursa. The diagnosis of textiloma was not in doubt and was based on the patient's previous surgical history and imaging findings. A surgical gauze sponge was removed through a limited laparotomy on the 16th day after the initial surgical intervention. However, later on, the patient was diagnosed with an abscess in the same area, caused by infected pancreatic necrosis and a gastroduodenal anastomosis fistula. Intensive conservative tratment resulted in a gradual improvement and spontaneous closure of the fistula. However, the patient's hospital stay lasted for a total of 73 days.

Case 13. A 60-year-old man had emergent surgery for acute large bowel obstruction due to an occlusive tumor of the sigmoid colon. He underwent the resection of the sigmoid colon and a terminal colostomy (Hartmann's procedure). The early postoperative period was complicated by diffuse abdominal pain, intestinal paresis, and high fever. Abdominal US was inconclusive, although it suggested an abscess. On CT scan, in the left upper abdomen, a slightly encapsulated mass with a spongiform pattern and multiple gas bubbles inside, measuring 109x85x125 mm in size, is visualized, along with infiltrative changes in adjacent tissues. Thus, 16 days after the primary procedure, a relaparotomy was performed with the removal of a foreign body (gauze sponge). There was a rapid disappearance of the pathological symptoms, and after 4 days he was discharged.

Results

Among the patients included in our study, the primary surgery was performed for urgent indications in 7 (53.8%) cases and in 6 (46.1%) cases on an elective basis. Females made up the vast majority—76.9%. During the analysis of case histories, other possible causes that could explain the unintentional leaving of textile foreign bodies in the abdominal cavity were also established, but they were not the purpose of this study and are not presented here. Only two patients had no pathological symptoms at the time of their textiloma diagnosis. The remaining 11 (84.6%) patients were symptomatic, with abdominal pain and a palpable mass being the most common manifestations.

Plain abdominal radiography and/or contrasted intestinal studies were performed in 9 cases, mainly to confirm or rule out the diagnosis of intestinal obstruction. The lesions did not show a definite pattern on radiographs, and in relation to textilomas, the studies were unremarkable. In only one patient (Case No.4), the radiologist noted an extensive area of homogeneous opacity that displaced bowel loops. In another patient (Case No.7), only a retrospective analysis of a contrast series made it possible to visualize an intraluminal textiloma as an oval structure covered with a barium mass. Finally, in case No.9, the X-ray contrast of a chronic purulent fistula opening in the postoperative scar suggested the presence of an abdominal foreign body.

Ultrasound scanning of the abdominal cavity was performed in 12 patients, except for one case with intestinal obstruction. In some cases, multiple scans were conducted. The presence of an intra-abdominal mass with a typical pattern of ultrasound visualization for textilomas was found in half of the cases (6 patients), which was characterized as a thick-walled hypoechoic mass with strong posterior acoustic shadowing. In four cases, the foreign body was characterized by the radiologist as an abscess, and in two more cases it turned out to be uninformative. However, abdominal ultrasound was not the ultimate diagnostic tool for determining indications for repeated surgery in any of the cases included in our series.

According to the CT results, a textiloma was found in the upper abdomen cavity, including the subphrenic and subhepatic spaces, in three cases; at the mesogastric level, in four cases; in the left and right iliac fossa, in three cases; and in the pelvic cavity, in three cases. The median size of the textiloma was 61x72x77 mm (anteroposterior x lateral x vertical length). The minimal volume of the lesion was 40x35x35 mm, and the maximal was 109x85x125 mm. In the majority of cases (n = 12), the lesion had a clearly defined oval or rounded shape. Only in patient No.10, who had less than 24 hours from the surgical intervention to the discovery of the foreign body, did the pathological mass appear to have an irregular shape. In eight cases (61.5%), the mass had a typical spongiform structure with numerous small air bubbles and was surrounded by a thin capsule. In the other four patients (30.8%), a high-density, well-circumscribed lesion was visualized without any air component inside, but sometimes with mottled calcification and a dense capsule with intense contrast accumulation. It is noteworthy that the interval from causal surgery until the diagnosis of textiloma was 1.71±0.6 months in the "spongiform structure" group, while in the "solid mass" group, it was 78.3±40.8 months. One patient (Case No.7) had an atypical CT scan presentation of a textile pad mimicking a barium mass in a small bowel loop and was diagnosed only during surgery.

Based on surgical history, physical examination, and CT scan findings, a likely diagnosis of textiloma was made before surgery in 11 of 13 cases (84.6%). In all patients, a repeated laparotomy was necessary to remove the textile foreign bodies. In most cases (n = 11), surgery was limited to simple gauze sponge retrieval, but in the other two cases, more complex reconstructive procedures were required, including segmental resection of the jejunal loop with end-to-end anastomosis (Case No.7) and closure of the ascending colon fistula (Case No.6). However, severe complications occurred in the early postoperative period in cases No.5, 7, and 12. These complications included sigmoid colon fistula, subcutaneous evisceration, and gastroduodenal anastomosis leak, respectively, which required intensive conservative treatment and resulted in a prolonged hospital stay.

Discussion

Textiloma is a medical condition defined as a textile foreign body that has been inadvertently left within the patient

and is discovered at any time after the patient exits the operating room [6]. The term "textiloma" is derived from "textilis" (tissue, cotton) in Latin and "oma" (tumor, edema) in Greek [7]. Other definitions of the condition in the medical literature include "gossypiboma", "gauzoma", "muslinoma", "cottonoid", and "cottonballoma" [1, 8, 9]. Retained foreign bodies belong to the category of "never events", which are caused only by human error and should not occur as they are easily preventable. However, if they do occur, they can lead to tragic consequences for the patient, causing increased morbidity and even mortality [4, 8].

Gauze sponges and pads are the most commonly left objects in patients' cavities and tissues due to their universal use during all surgical procedures, relatively small size, and amorphous structure, especially when they soak up and become saturated with blood and other liquids [1, 5]. Most often, textilomas were found in the abdominal cavity, a fact explained by the complexity of its anatomy and its large volume [1, 2]. The incidence of abdominal textilomas is not known, and most publications are limited to reports of single cases or small series, due to possible legal and/or reputational implications for the hospital and surgeons involved [2]. However, according to the most reliable data, the incidence of abdominal textiloma is estimated to range from 1 in 1,000 to 1 in 1,500 for intra-abdominal operations [10, 11].

Any foreign object elicits a reaction in the human body [9]. The manifestations of this reaction, as well as the natural evolution of foreign textile items unintentionally left in the human body after surgery, are variable and depend on the item's location, composition, grade of bacterial contamination, and the individual host's response. Patients with textiloma can have two main types of foreign body reactions [3, 4, 7]. The most common is an aseptic fibrous inflammatory reaction and adhesion that encapsulates the textile item in the omentum and surrounding organs. These patients usually remain asymptomatic and are discovered incidentally, as happened in cases No.3 and 8 in our series, or have very limited and non-specific symptoms, dominated by general malaise, vague pain, and sometimes a palpable abdominal mass (cases No.1, 2, 5, and 11). The second known reaction is of the exudative-inflammatory type, which leads to the formation of an abscess or purulent fistula. This reaction usually manifests acutely, in the early postoperative period or much earlier than the fibrinous reaction [12], in the form of persistent inflammation and local septic complications (cases No.4, 9, 12, and 13). The most threatening evolution of textiloma is associated with the gradual erosion of the bowel wall due to a combination of mechanical pressure and localized inflammation. The final part of this process is the bowel wall destruction, with partial or complete migration of the gauze sponge into the intestinal lumen. In our series, colonic fistula development was documented in two cases (No.5 and 6). However, in patient No.7, the textiloma completely migrated into the jejunal lumen, causing acute intestinal obstruction.

In any case, clinical signs are often nonspecific, and the possibility that a foreign body was left behind is rarely considered when assessing the postoperative course, particularly in the early stages. Therefore, imaging studies play a decisive role in making a timely diagnosis. Conventional radiography is the standard method for the initial diagnosis of acute abdominal abnormalities, including the detection of remaining sponges [13]. The exam is especially effective if the gauze sponge has a radiopaque marker, which is in line with universal surgical recommendations [1, 14]. Unfortunately, the use of radiopaque markers on surgical sponges is inconsistent in the Republic of Moldova. In our series of thirteen patients, all of whom had their primary surgeries in different hospitals across the country, none of the surgical sponges had a radiopaque marker. This made it difficult to visualize them during imaging studies. In some cases, a plain abdominal X-ray may reveal a faint soft tissue density with mottled lucencies due to trapped air or abscess formation. While this finding may raise suspicion, it cannot confirm the diagnosis of textiloma with certainty [4].

On abdominal ultrasound, textilomas typically appear as well-defined masses that can be either cystic or solid. Ultrasound features typically include a wavy internal echogenic source with a hypoechoic rim and a dense posterior shadow [4, 13, 15]. Posterior acoustic shadowing is the most characteristic sonographic feature of textilomas and may result from the retained sponge or from areas of calcification or air within the mass [13, 15]. However, ultrasonography has some limitations, such as operator dependence, difficulty identifying foreign bodies at greater depths or located posteriorly to a gas-containing hollow viscus, and the possibility of presenting false-positive results in cases where scars and calcifications of other etiologies are present [13]. Of the 13 patients in our series, only 2 ultrasound scans were completely uninformative. In the remaining patients, a "volume mass' was visualized or an "abdominal abscess" was suspected. However, in no case did the examiner definitively identify the lesion as a "retained foreign body." This could be because radiologists may not receive adequate training or have enough experience in recognizing surgical sponges, and therefore may lack complete information about what these objects might look like. As a result, the abdominal ultrasound data in our study were inconclusive and only indicative and could not be used to justify a diagnosis or further therapeutic measures. Additionally, ultrasound scanning was not able to provide information on the anatomical relationships of the textiloma.

In cases of abdominal textiloma, a CT scan may be indicated in the presence of indeterminate or non-specific clinical manifestations, or in the presence of predisposing findings from previous examinations. On CT, the most characteristic feature of a textiloma is a heterogeneous, low-density cystic lesion with a typical spongiform pattern resulting from trapped gas bubbles, surrounded by a thin, high-density capsule that exhibits marked enhancement after contrast administration [4, 12, 16]. In chronic cases, the gas bubbles within the retained gauze piece are gradually absorbed, and the textiloma acquires the visual characteristics of a round or oval soft-tissue-density mass with a thick

capsule, strong wall enhancement, and calcifications [15]. The latter is often defined as a so-called "calcified reticulate rind" sign, which is probably formed by gradual deposition of calcification along the fiber network of the surgical gauze [17]. In our study, we observed both acute and chronic CT appearances of textiloma, with these features closely related to the disease duration. The acute form was typically detected after an average of two months, while the chronic form was found after an average of 78 months. Importantly, in all cases, regardless of the clinical manifestations and duration of the disease, CT scanning was the decisive imaging method, allowing for the identification of a mass related to a foreign body and the establishment of an accurate diagnosis of textiloma, including its anatomical location, the presence of possible complications, and the need for repeated surgical intervention.

Once a textiloma is diagnosed, surgical removal should be performed even if the patient is asymptomatic to prevent potential complications that could lead to a high mortality rate [2, 4, 8]. In our series, most patients were symptomatic, and all cases of textiloma were surgically removed through open laparotomy. While most surgeries were technically simple and involved only the retrieval of the foreign body, two patients required more complex reconstructive procedures. Furthermore, the postoperative course was challenging for three patients, requiring prolonged hospitalization. However, all of these repeated surgeries could have been easily avoided with timely detection and removal of the retained sponges.

Undoubtedly, prevention is the best treatment modality for textile foreign bodies forgotten in the abdominal cavity. Many systems and safeguards are applied in the operating room to ensure that no material is left behind unintentionally after closure [1, 2]. The most common recommendations include creating a well-organized operating room with minimal distractions, ensuring optimal communication among the surgical team and support staff, and strictly adhering to patient safety measures, which are maintained by carefully, consistently, and informally following all the rules of the "Surgical Safety Checklist" developed by the World Health Organization in 2009 [14]. Counting items at the time of surgery is the most widely used method for the screening of textile surgical objects, with established protocols in place. In fact, the process by which counts are performed is not standardized and is often modified according to individual hospital policies. At the end of 2022, the Ministry of Health of Moldova approved the National Guidelines for "Safety of Surgical Patient in the Operating Room", which, among other things, provides clear recommendations on standard rules for counting gauze sponges and other surgical objects during surgery [18]. It provides four separate counts during each operative procedure: (1) before surgery begins; (2) before closure of any hollow organ; (3) before closure of a laparotomic wound; and (4) during suturing or closure of the skin. In addition, the movement of all surgical objects and instruments should be closely monitored throughout the operation, and the surgeon should carefully explore the abdominal cavity for foreign bodies, regardless of the final count results. In accordance with international standards, the Guidelines strongly recommend the use of only surgical textile materials with an incorporated radiopaque marker in open body cavities [14, 18]. Of course, the latter measure does not prevent inadvertently leaving gauze sponges in the abdominal cavity, but in cases of inconsistency in their count before closure, intraoperative radiography of the entire surgical field makes it easy to identify the lost object.

Conclusions

Our study showed that despite increased attention to patient safety, textiloma is still encountered in daily surgical practice. The possibility of an abdominal textiloma should be considered in the differential diagnosis of any postoperative patient who presents with pain, infection, or a palpable mass.

The CT scan is a practical and highly sensitive diagnostic tool for detecting abdominal textilomas with characteristic imaging features in both chronic encapsulated and acute inflammatory manifestations.

Prevention of abdominal textiloma can be achieved with increased vigilance and strict adherence to preventive measures and strategies in the operating room, aimed at a careful count of sponges and instruments as well as thorough cavity exploration.

Competing Interests

None declared.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Authors' contributions

Concept and design of study – SG, IrC; acquiring of data – OG, DZ, IuC, ID; analysis and/or interpretation of data – SG, IrC, OG, DZ, IuC, ID; drafting the manuscript – SG, IrC; revising the manuscript critically for important intellectual content – SG, IrC. All authors have read and approved the final version of the manuscript.

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RESEARCH STUDY

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Preterm birth prediction in pregnant women over than 35 years. Observational analytical cohort study

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ABSTRACT

Introduction. Premature birth can occur at any age; however, it is important to note that the risk of preterm birth can vary based on several factors, including the mother's medical history, general health, and lifestyle. There is thought to be a relationship between maternal age and the risk of preterm birth, although the exact nature of this relationship may vary. At the same time, it is considered for ages over 35, an increased risk factor for the evolution of pregnancies with complications. Pregnant women over 35 face a higher risk of premature birth. This increased risk may be associated with age-related factors such as underlying health conditions, higher rates of multiple pregnancies (due to fertility treatments), and potential placental dysfunction.

Material and methods. In the given study, the biomarkers IL-6, IL-8, IL-10, IL-12, SDF-1α and VEGF in amniotic fluid (AF) and maternal blood were investigated, considering the above as predictive of premature birth outcome. At the same time, the oxidative stress status of maternal blood and amniotic fluid collected in the second trimester of pregnancy was identified.

Results. In the research, we obtained statistically significant increases in the biomarkers AAT-isopropyl, G-GTP, HPL-isopropyl from the amniotic fluid taken from pregnant women over 35 years of age in the second trimester of pregnancy in those pregnant women who had a preterm birth. In the serum of pregnant women with premature birth, an increase in the concentration of carnosine-histidine peptides, G-GTP, GR and SH (thiol) groups was identified, and the decrease in the values of SDF 1α, HPL – hexane and IL-12 were statistically significant in the serum pregnant women compared to that of the amniotic fluid.

Identifying the values of biochemical mediators during pregnancy can be a method of predictive diagnosis

Conclusions. Our study shows the relationship between some concentrations of oxidative stress biomarkers (AAT-isopropyl, HPL-isopropyl and G-GTP, IL-12) in amniotic fluid, and values of (Carnosine Histidine Peptide, GR and SH and SDF-1α) in the serum of pregnant women, in the second trimester of pregnancy.

Keywords: premature birth, preterm delivery, risk factors, pregnancy over the age of 35 years, cytokines, inflammation, biomarkers, IL-6, IL-8, IL-10, IL-12, SDF-1α, VEGF, oxidative stress, amniotic fluid.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Premature birth can be associated with a number of complications and risks for both mother and baby. Babies born prematurely may have breathing difficulties due to the immaturity of their lungs, which could diminish their quality of life.

Immune biomarkers, determined from the blood of pregnant women over 35 years of age and from the amniotic fluid, are informative with predictive value for pregnancies ending in premature birth.

The research hypothesis

Observational analytical cohort study in preterm birth prediction in women over than 35 years from the second trimester of pregnancy by investigating the correlation between the level of oxidative stress and cytokines in fetal amniotic fluid (AF) and maternal blood, taken in the second trimester of pregnancy in pregnant women aged over 35 years at which the premature birth was subsequently certified.

The novelty added by manuscript the already published scientific literature

Following the results received in the study, the identified immune mediators were found to be involved in the prediction of pregnancy complications, due to premature birth. Importance multifunctional of cytokine, involved in the immune response mechanisms, in the case of the given study it is associated with the complication of pregnancy through preterm birth in women over than 35 years.

Introduction

Premature birth is one of the main causes of perinatal morbidity and mortality [1-3]. For women with pregnancy over 35 years, the risk of pregnancy complications is worrying.

It is considered one of the main causes of maternal morbidity, and it refers to the presence or occurrence of diseases conditions, or health complications [4, 5].

In recent years, in the Republic of Moldova, there is a tendency to postpone pregnancy after the age of 35 [6, 7].

With age, the woman's body is more susceptible to chronic pathological manifestations, medical complications during pregnancy in pregnant women over 35 years of age are determined by the aging of the reproductive system, which includes the increased risk of complications during pregnancy.

One of the complications during pregnancy and birth is hemorrhage, which is often due to premature births. Anticipating the pathologies of the pregnancy evolution, as well as an early diagnosis of the pathologies that complicate the pregnancy evolution would significantly influence the prognosis of maternal risk in pregnancy [6].

Premature birth is one of the main causes of perinatal morbidity and mortality. For women with pregnancy obtained through the in vitro fertilization method, over 35 years old, the risk of pregnancy complications is worrying.

It is considered one of the main causes of maternal morbidity, and it refers to the presence or occurrence of diseases, conditions or health complications

Numerous studies have identified the role of oxidative stress and cytokines in the pathogenesis of preterm birth [7, 8].

The purpose of the study: to identify the correlation between preterm birth and the level of oxidative stress in fetal amniotic fluid and maternal serum collected in the first trimester of pregnancy in pregnant women over 35 years old.

Materials and methods

A clinical trial has been performed in the National Center of Reproductive Health and Genetics in the Republic of Moldova and has included the pregnant women after 35 years, who have been subjected to an invasive prenatal diagnosis (amniocentesis). According to the pregnancy outcome, from a cohort of 65 women, which were divided into 2 groups: the first group of pregnant women over 35 years (37.8±0.48), the study group, was made up of 11 patients who have been included in the group with premature birth, and second group control from 35 to 37 years old (36.4±0.83) who had no complications in pregnancy.

The study has been approved in 20 June 2011, by the "Research ethics committee of State University of Medicine and Pharmacy *Nicolae Testemitanu"*, created by Senate Decision no. 6/1 of August 30, 2010 in accordance with the provisions of the National Legislation. An informed consent has been obtained from each subject at the beginning of the study.

Amniocentesis and blood samples: The intervention has been performed aseptically, transabdominal ultrasound-guided, 20 ml of amniotic fluid has been extracted first for the further diagnostic tests according to the cytogenetically screening, subsequently 10 ml of amniotic fluid has been removed and divided into 2 ml aliquots and stored at -48°C until being analyzed.

The venous blood has been collected after the amniocentesis procedure and drawn into the specimen tubes for serum extractions and tubes containing EDTA as anticoagulant for plasma extractions. The plasma and serum have been prepared by centrifugation, aliquoted and stored at -48°C until being analyzed.

Assay of serum and amniotic fluid cytokines IL-6, IL-8, IL-10, IL-12, SDF-1a, VEGF, concentrations have been measured by specific quantitatively affordable enzyme linked immunosorbent assay (ELISA) kits (PeproTech Inc., Minneapolis, USA.) according to the manufacturer's instructions. The assays have been carried out in flat-bottomed 96-well immunoplates (MaxiSorp, Nunc, Wiesbaden, Germany). The amniotic fluid and serum have been measured using BioTek's PowerWave HT microplate spectrophotometer. A standard curve has been made in parallel to each assay and the results have been converted into pg/mL.

Oxidative stress markers were also analyzed: AAT%-hexane, AAT-isopropyl, HPL-hexane-early, HPL-hexane-late, HPL-hexane-intermediate, HPL-isopr-early HPL, HPL-isopr-intermediate, DAM, NO, Histidine peptides Carnosine,

Catalase, ROS, G-GTP, Total proteins, Albumin, PPOA,Thiol groups of prot, Thyoredoxin, Glutaredoxin, AIM, GR, K, Ca, G-S-T, AGE, S-nitrosothiols, GPO, SH groups, He had dammed.

The analysis of the obtained data was performed on a personal computer using standard programs such as Microsoft Word 2010, Microsoft Excel 2010, Statistica 10. The qualitative indicators were analyzed using the non-parametric method - the calculation of the Chi-square test, which allows to evaluate the statistical significance of the differences between two or more relative measures and the Chi-square corrected by Yates for continuity.

Results

In a cohort of 65 pregnant women over 35 years old examined in the present study, 11 developed premature births.

Examining the biomarkers of both groups, up to 21 weeks of gestation, proved informative. Of all the cases investigated, the take-off premature birth were registered in the term after 35 weeks of gestation and resulted in premature birth.

No specific difference was found between the groups included in the study the stage of the second trimester of pregnancy related to the obstetric and anamnestic antecedents of pregnant women over 35 years.

Although many studies have shown that elevated levels of cytokines and oxidative stress may be associated with an increased risk of preterm birth in certain situations, such as intrauterine infections, cervical and amniotic sac inflammation, or complications such as preeclampsia.

In the blood serum taken from the pregnant women in the given study, who later developed premature birth, an insignificant increase of the following markers was attested: The level of cytokine biomarkers IL-6, from the blood of the pregnant woman (score 0.108, p = 0.742), IL-6, from the amniotic fluid (score 1.3930, p = 0.238), the level of IL-8, from the blood of the pregnant woman (score 0.018 , p = 0.892), IL-8, from the amniotic fluid (score 1.837, p= 0.175), IL-10 level, from the blood of the pregnant woman (score 0.594, p = 0.441). Nevertheless, there has been no difference between IL-10 levels in the AF in both groups, and the average value has been approximately equal. IL-10, from the amniotic fluid (score 3.418, p = 0.065), IL-12 level, from the blood of the pregnant woman (score 0.015, p = 0.903), IL-12, from the amniotic fluid, however, proved to be statistically informal (the score 4.229, p = 0.04) in the research group its level was found to be increasing.

Oxidative stress is an imbalance between the production of reactive oxygen species (ROS - reactive molecules that include hydrogen peroxide, free oxygen radicals, and other similar molecules) and the ability of the body's antioxidant system to neutralize and repair these ROS.

Oxidative stress can damage fetal membranes, which are responsible for maintaining the integrity of the amniotic sac. If the membranes break prematurely, premature rupture of the membranes (water breaks) can occur and premature birth can occur. At the same time, oxidative stress can stimulate the release of inflammatory cytokines, such as interleukins, which can trigger inflammatory processes in the uterus. This inflammation can lead to premature uterine contractions and trigger premature labor.

The value of SDF-1α in the serum of the pregnant woman is statistically significant (value of 6.838 p =0.009) but SDF-1α in the amniotic fluid (value 3.001 p = 0.083), with the statistical value for the given study insignificant. Biomarker VEGF - in pregnant serum was not significantly different between the given groups (value 1.030 p = 0.310) and in the amniotic fluid it was not statistically informative either VEGF (value 1.762 p = 0.184).

This is why we also studied markers of oxidative stress to identify the possibility of predicting premature birth in the second trimester of pregnancy (Table 1).

Table 1. Statistical variable in the amniotic fluid and blood of pregnant women taken in the second trimester of pregnancy

	Value	Statistical significance	Value	Statistical significance
Researched marker	Serum of pregnant women		Amniotic fluid	
AAT%- hexane mM/s.l	2,116	p =0,146	0,466	p =0,495
AAT-isopropyl mM/s.l	0,640	p =0,424	4,093	p =0,043*
HPL-hexane-time uc/ml	0,046	p =0,830	8,564	p =0,003**
HPL-hexane-intermediate uc/ml	0,336	p =0,562	3,015	p =0,082
HPL-hexane-late uc/ml	0,001	p =0,975	0,942	p =0,332
HPL-isopr-time uc/ml	3,117	p =0,077	3,351	p =0,067
HPL-isopr-interm uc/ml	3,562	p =0,059	3,983	p =0,046*
HPL-isopr-late uc/ml	2,269	p =0,132	2,693	p =0,101
DAM μM/l	1,449	p =0,229	3,785	p =0,052
NO μM/l	2,892	p =0,089	0,599	p =0,439
Histidine peptides Carnosine μM/l	6,898	p =0,009**	0,005	p =0,944
Catalase μM/l	0,172	p =0,678	1,567	p =0,211
SOD u/c	1,402	p =0,236	2,647	p =0,104
G-GTP U/L	4,535	p =0,033*	3,829	p =0,050*
Prot all g/L	0,418	p =0,518	0,876	p =0,349
Albumin g/L	1,265	p =0,261	1,486	p =0,223
PPOA	1,306	p =0,253	0,063	p =0,802
Thiol groups of protein	0,777	p =0,378	2,375	p =0,123
Thyoredoxin	0,036	p =0,850	0,429	p =0,512
Glutaredoxin	2,360	p =0,124	1,597	p =0,206
GRM/s.L	0,523	p =0,469	4,829	p =0,028*
K mM/L	0,054	p =0,817	0,075	p =0,784
G-S-TμM/min. IT	0,024	p =0,876	0,163	p =0,686
AGE μg/L	1,117	p =0,291	0,747	p =0,387*
SH groups, mkM/g protein	9,019	p =0,003**	-	-

Note: AAT - total antioxidant activity; HPL - lipid hydroperoxides; DAM - malonic dialdehyde; NO - nitric oxide; SOD - superoxide dismutase; G-GTP - γ Glutamyltransferase; Prot – protein; PPOA - protein products of advanced oxidation; GR - glutathione reductase; K – Potassium; G-S-T - glutathione-S-transferase enzyme; AGE - advanced glycated end-products; SH groups - thiol group * - p <0,05, ** p <0,001**

A tendency to decrease IL-12 concentration (4.229, p=0.04) was found in the group with the risk of premature births. At the same time, SDF-1α biomarkers were also de-

creased in the serum of the pregnant woman, statistically significant (value of 6.838 p =0.009). Early hexane HPL in the amniotic fluid collected in the second trimester of pregnancy (8.564, p =0.003**), unlike AAT-isopropyl in the amniotic fluid whose value increased in the studied group (4.093 p =0.043*), HPL-isopropyl- intermediate also had a tendency to increase in amniotic fluid in the second trimester of pregnancy in pregnant women over 35 who were going to develop premature labor (3.983 p =0.046*). As well as the values of carnosine histidine peptides, from the single pregnant woman, G-GTP and from the pregnant woman's serum, and from the amniotic fluid sampled, GR and SH thiol groups from the sampled serum, with statistically significant values.

Discussion

The increased risk of preterm birth among older mothers is largely explained by early induction of labor for medical conditions. Our study contributes to the identification of variables, the testing of hypotheses and the attempt to predict certain particularities in the evolution of pregnancy, which may occur in pregnant women over 35 years old.

The study was based on a cohort of 65 pregnant women over 35 years of age who had indications for amniocentesis at 16-21 weeks of gestation.

The aim of the research was to confirm the hypothesis of the existence of a correlation between the risks of pregnancy evolution through premature birth and immune biochemical markers in pregnant women over 35 years old. Biochemical markers were collected from maternal serum and amniotic fluid during the second trimester of pregnancy.

In a series of researches, many authors have developed statistical predictive models of premature birth [9-11]. Other studies focus on clinical characteristics, which could be predictors in preterm birth [12-15].

Besides predicting the risk of premature birth, its prevention is of major importance, because it is very complex, it remains open for further research.

The variety of methods used to measure, for example, oxidative stress is great. Many authors such as Ferguson K., Gunko V. O., Abiaka C., Machado L. in their studies, determine biomarkers by different methods [16-18].

There are also reports of some studies on the importance of immune (interleukin), vascular (VEGF) markers in predicting the evolution of pregnancy with risk of premature birth [19, 20].

At the same time, all these methods are considered to be quite difficult, since oxidative stress biomarkers are very reactive and have very short half-lives. The reason it may appear both in our study and in other hypothesis-based studies of preterm birth risk prediction is that the results of the studies depend on the method used and how quickly these data are measured.

Validation of results identified in adjacent studies is difficult to determine due to the lack of a typical standard for establishing research methods [21].

The study analyzed the panel of markers related to maternal immune response in the second trimester of pregnancy, cytokines, angiogenesis and oxidative stress, in association with the evolution of preterm birth.

For this, samples were determined from the amniotic fluid collected from pregnant women over 35 years old in the second trimester of pregnancy and from the maternal serum, during the same period of time.

In amniotic fluid we obtained statistically significant increases in AAT-isopropyl, G-GTP, HPL-isopropyl.

In the serum of the pregnant woman, the increase in the concentration of carnosine-histidine peptides, G-GTP, GR and SH (thiol) groups was identified, and the decrease in the values of SDF-1α, HPL – hexane and IL-12 were statistically significant in the serum of the pregnant woman compared to that of amniotic fluid.

Identifying the values of biochemical mediators during pregnancy can be a method of predictive diagnosis.

Immunological and inflammatory factors evaluated in pregnant women over 35 years suggest their importance in predicting the occurrence of early miscarriages at the molecular level.

Carrying out research on the behavior of the values of immune mediators in human amniotic fluid and maternal plasma, in pregnancies that ended with premature births compared to physiological births, the aim was to understand the metabolism that takes place during the period of high-risk pregnancy. This allows to select markers, which will be able to be used as rapid tests to identify patients at risk of premature birth.

Currently in the Republic of Moldova, the diagnostic algorithm for patients with imminent or premature labor includes the test: detection of fetal fibronectin (fFN) - a glycoprotein present in the amniotic fluid, placental tissue, which has a predictive value in pregnant women who are at risk of imminent birth premature [22]. The positive prediction, however, is modest (< 20%), because most women have a good outcome because they are treated.

Precisely for these reasons, the World Health Organization (WHO) declares in research priorities during pregnancy, with the aim of reducing the rate of premature births, including epidemiological studies related to the identification of the causes of premature birth, understanding the mechanisms that lead to the initiation of labor, the development of simple screening tests, based on biological and genetic findings with the aim of identifying pregnant women at high risk of labour. Thus, the conducted study falls within the level of research, which presents the scientific value in reducing premature births [23].

Conclusions

This study demonstrates the involvement of immune biomarkers for pregnancies that ended through preterm birth by increasing the concentration of AAT-isopropyl, HPL-isopropyl and G-GTP in amniotic fluid, while decreasing the concentration of IL-12 in amniotic fluid. In the blood, the increased values of Carnosine Histidine Peptide, GR and SH in the serum of pregnant women, as well as the biomarker SDF-1α, in the second trimester of pregnancy.

The predictive value of these markers for pregnancies with risk of premature birth in pregnant women over 35 years of age is of interest for further research.

Abbreviations

AAT – total antioxidant activity; HPL – lipid hydroperoxides; DAM – malonic dialdehyde; NO – nitric oxide; SOD – superoxide dismutase; G-GTP – γ Glutamyltransferase; Prot – protein; PPOA - protein products of advanced oxidation; GR - glutathione reductase; K – Potassium; G-S-T – glutathione-S-transferase enzyme; AGE – advanced glycated end-products; SH groups - thiol group, AF – amniotic fluid; IL – interleukin; SDF-1α – Stromal cell-derived factor 1α.

Competing interests

None declared.

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RESEARCH ARTICLE

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The joint ultrasound markers in the early diagnosis of psoriatic arthritis

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ABSTRACT

Objectives. Early establishment of arthritis in PsA based on clinical data and ultrasound examination.

Material and methods. The study was conducted between 2019-2023, in the rheumatology and arthrology departments of the *Timofei Moșneaga* Republican Clinical Hospital, or treated in outpatient. In order to meet the requirements of the study, 100 people were examined, including 70 patients with PsA.

Results. In patients with PsA the most common changes were an increase in the amount of intra-articular fluid and the proliferation of the synovial membrane. In total, fluid was detected in 293 out of 3,232 joints (9.1%).

Conclusions. Ultrasound is a highly informative method in detecting a wide range of morphological changes in the joints of patients with PsA. The highest index of sensitivity appeared when inflammatory fluid, cartilage changes, osteophytes and tenosynovitis were detected.

Keywords: psoriatic arthritis, early diagnosis, joint ultrasonography.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

It is especially interesting to determine the early diagnosis of psoriatic arthritis (PsA) based on clinical data and by ultrasonographic research.

The research hypothesis.

This article aims to present the interrelation between early manifestations in PsA and ultrasound diagnosis.

The novelty added by manuscript to the already published scientific literature.

For the first time, the possibilities of ultrasound in the differential diagnosis of PsA and RA as a disease, which is based on proliferative changes in the synovial membrane, are grounded.

Introduction

Psoriatic arthritis (PsA) is one of the most important diseases of great medical and social importance, due to its progressive and significant takeover, which can lead to early disability. The prevalence of psoriatic arthritis is evidenced in the age range of 20-50 years, and both sexes are equally affected. PsA usually has a violent progression with osteo-articular mutilation.

The diagnostic challenges in early PsA are not limited to the heterogeneity of the disease, which stands out from the variety of measures available for the outcome [1]. Unlike RA, there are no biomarkers such as cyclic citrulline anti-peptide antibodies or rheumatoid factor (RF) to identify early PsA, and therefore the diagnosis depends on the identification of specific clinical characteristics. In addition, the increase in acute phase markers such as C-reactive protein (CRP) occurs only in up to half of patients and therefore has a limited value in early PsA [2]. Finally, the absence of skin psoriasis in the presence of arthritis can lead to a label of undifferentiated arthritis. Reflecting these deficiencies, imaging has been increasingly used for PsA evaluation and therapy [3].

Common symptoms of inflammatory arthritis may include swelling of the joints, hyperemia, prolong morning stiffness (0.5-1 hours) and X-ray evidence of bone damage in juxta-articular [4, 5]. The number and type of joints involved (for example, small vs. large) and their appearance (e.g. symmetrical vs. asymmetrical) can also be similar between arthritis [6-8]. In addition, unique manifestations of the disease, such as enthesitis and dactylitis, can be difficult to detect clinically [9]. Moreover, serologies can fail to conclusively differentiate these diseases, and the increase in acute phase reactants is nonspecific [10-13].

In early disease and in patients with milder symptoms, in whom the clinical findings are not definitive, imaging is necessary to accurately differentiate the types of inflammatory arthritis. The recommendations of the European League Against Rheumatism (EULAR) for the management of early arthritis are guided by a general principle that "*a definitive diagnosis in a patient with early arthritis should be made only after a careful anamnesis and a comprehensive clinical examination, which should guide laboratory tests and additional instrumental procedures*" [14].

USG has various advantages, including higher accessibility, low overhead costs, lack of contraindications and its availability in the clinic. The criteria obtained for the ultrasound diagnosis of joint lesions in PsA will contribute to the timely and effective diagnosis of the disease, and therefore to the importance of adequate therapy. The use of Doppler techniques will allow to evaluate the activity of arthritis, as well as to monitor therapy with basic drugs.

Material and methods

One hundred people were examined, including 70 patients with PsA aged between 18 and 60 years, of which 23 men and 47 women who were undergoing treatment, admitted to the rheumatology and arthrology departments of *Timofei Moşneaga* Republican Clinical Hospital or treated in outpatient during 2019-2023 (favorable opinion of the Committee for Research Ethics at no.21 of 21.12.2019). The comparison group included 30 people with rheumatoid arthritis.

The patient was considered included in the study after signing the informed consent form and all of them were corresponded to including criteria: CASPAR diagnostic criteria (2006). There were 28 patients with polyarticular form of PsA (40.0%) and 29 with mono-, oligoarthritis (41.4%), which presented with the same frequency. In 18.6% (n = 13) of the observations, damage to the distal joints of the hands and plants was detected. Mostly were appreciated minimal (n=31; 44.3%) and average (n=24; 34.3%) disease activity. Patients with a high disease activity (n=12; 17.1%) and patients in remission (n=3; 4.3%) were in a few numbers.

The reference group consisted of 30 patients with rheumatoid arthritis aged 27 to 63 years (average age 45±12.3 years) with disease evolution from 6 months to 32 years (average 12±5.4 years). Patients in both groups were comparable by age and evolution of the disease. All patients underwent ultrasound Power Doppler examination of the knee joints and the joints of the hands and plants (n=2320).

The analysis of the obtained results was carried out using standard statistical methods (Mann-Whitney criterion, criterion X^2, Fisher criterion). The differences were considered significant at $p<0.05$.

Results

Ultrasound examination was the main method in the complex diagnosis of PsA. The results of the study demonstrated that in patients with PsA, damage to all anatomical structures of the joint with polymorphism of the ultrasound pattern is detected.

The most common changes in the joints in patients with PsA were an increase in the amount of intra-articular fluid and the proliferation of the synovial membrane. The appearance of fluid in the joints occurred in the overwhelming number of patients (n = 63.90%) and only in 10% (n = 7) of the observations there was no inflammatory liquid. In total, fluid was detected in 293 out of 3,232 joints (9.1%). Among the knee joints in which there was an increase in the amount of intraarticular fluid (n = 79; 100%), in 48.8% (n = 37) of the observations were joints with a small amount of fluid (gradation 1). In a smaller number, the amount of liquid corresponding to grade 2 (n = 24; 30.4%) and grade 3 (n = 18; 20.8%) were observed. In the radiocarpal joints, the maximum thickness of the liquid in the joints was 6 mm, in the ankle joints – 8 mm. The maximum thickness of the fluid in small joints was 2 mm. In our study, homogeneous effusion into the joint cavity prevailed (n=201; 68.6%). The heterogeneity of the structure (n=92; 31,4%) was due to the appearance of partitions, suspensions or hyperechogene solid inclusions against the background of anechogenic contents.

Magnetic resonance imaging was the second method of investigation in the complex diagnosis of PsA and was used as a reference method. In the study group, fluid was the predominant symptom in frequency (n = 13, 92.86%), including in the small joints of the hands and legs. Syno-

vial proliferation was the second most common sign of damage to the knee joint (n = 10; 71.43%) and was detected in 3.6% of the foot joints and 7.1% of the joints of the hands. The signal intensity of the synovial layer in the overwhelming number of observations was in the isointensive liquid T1, in T2 - medium intensity and slightly above the liquid - in FSat mode. In one of the observations, when the synovial membrane was not vascularized according to ultrasound data, its intensity in T1 and in FSat was significantly lower than the signal from the liquid and practically merged with the surrounding tissues. In this case, the synovial membrane is visualized in T2 and FSat due to a low-intensity border that separates the synovium from the fluid on the one hand and from the surrounding tissues on the other.

In our study, erosions were detected in 3 joints and localized in the condyles of the femoral and tibial bones and in the ends of the metatarsal bones II and III of all surfaces. The changes in cartilage consisted of its thinning and structural changes and were observed in 28.57% of cases (n = 4). In one observation, fragmentation of cartilage occurred, in the other, changes in the type of cracking were revealed, falling into the manifestations of chondromalacia.

As MRI was chosen as the reference method for correctly evaluating the diagnostic efficacy of ultrasonography in detecting existing changes, MRI results obtained in 15 patients in 56 joints were compared with ultrasound data of the same patients (Table 1).

Table 1. Comparison of signs, viewed at USG PD and MRI, in 16 patients

Symptom	Number of joints with detected changes		p
	USG PD	MRI	
Liquid	16 (28.6%)	16 (28,6%)	>0.05
Proliferation of synovial membrane	11 (19.6%)	12 (24.1%)	<0.05
Cartilage changing	4 (7.1%)	4 (7.1%)	>0.05
Bone erosions	2 (3.5%)	4 (7.1%)	<0.05
Osteophytes	7 (12.5%)	7 (12.5%)	>0.05
Degenerative changes in tendons	6 (42.9%)	7 (50%)	<0.05
Tenosynovitis	3 (5.4%)	3 (5.4%)	>0.05

Note: USG PD – UltraSonoGraphy Power Doppler, MRI - Magnetic Resonance Imaging, p – criteria t-Student

Over our study evolution, ultrasonography and clinical and laboratory activity data were compared for all joints as a whole. The results of correlation analysis show a positive correlation between the severity of ultrasound symptoms of synovitis and the level of clinical and laboratory markers of inflammation. At the same time, the ultrasound symptom, which mostly correlates with the level of local activity, is the degree of vascularization of the synovial membrane, which appeared both in the large joints (r = 0.508) and in the small ones (r = 0.500). The strongest correlation is observed between the amount of fluid (r = 0.401) and degree of vascularization of the synovial membrane in the knee (r = 0.508), small joints (r = 0.500) and the level of ESR, CRP and leukocytosis. A weaker correlation is observed between the level of laboratory markers and the thickness of the synovial membrane (r = 0.383).

Discussions

Thus, psoriatic and rheumatoid arthritis are similar in morphology and clinical evolution of disease. When comparing the frequency of occurrence of distinctive signs at USG PD of damage to the knee and small joints, depending on the nosological affiliation, the following results were obtained by us and the same results had been presented by literature data [3, 6, 7, 14]. In the group of patients with PsA, enthesopathy and enthesitis of their own patellar ligaments and tendons of the femoral quadriceps were detected significantly more often, then in case of RA.

Data from the literature, as well as our study, determine that the lesion of the small joints of the hands and plants is characterized primarily by diffuse proliferation of the synovial membrane, mainly with low echogenicity (p =0.0001), which in 92% of cases is accompanied by a homogeneous effusion (p = 0.005). Changes in the ligamentar apparatus in all observations are represented by tenosynovitis. From the literature data it is known that the low echogenicity of the synovial membrane is due to its edema against the background of active inflammation, and this pattern was reflected in the clinical picture of the lesion of the small joints of the hands and plants in our study too [4, 6, 8, 10]. It remains unclear the frequent detection of the synovial membrane, mainly with high echogenicity, in the knee joints, independent of the activity of the disease. Perhaps this fact is due to the earlier fibrosis of the synovial membrane in this localization [1, 3, 13].

Remain unclear the differences between PsA and RA expresses' in small joints: the examination of small joints in patients from PsA group, inflammatory fluid was detected more often than in patients from RA group (p = 0.009) [4, 5, 11]. But patients with RA, a feature of the visual picture was more frequent detection of proliferative changes in the synovial membrane in both the knee joints (p = 0.03) and in the small ones (p = 0.001), compared to PsA, this fact was marked by other authors [6, 8]. Statistically there were no significant differences in the frequency of detection of inflammatory fluid in the knee joints, tenosynovitis, the nature of joint effusion and changes in cartilage structure in patients with PsA and RA.

As in other studies, the analysis depending on the lasting changes in the disease detected by USG PD demonstrated that marginal bone growths are just as often detected in a group of patients with the duration of the disease more than 10 years, regardless of nosology [3, 7, 12]. Thus, the study carried out showed the effectiveness of the ultrasonographic method in detecting morphological changes in the joints in patients with PsA, determining the activity and evaluating the results of treatment.

Conclusions

1. Ultrasound is a highly informative method in detecting a wide range of morphological changes in the joints of patients with PsA. The highest sensitivity markers occurred when inflammatory fluid, cartilage changes, osteophytes and tenosynovitis were detected. Less sensitivity markers were achieved in the

detection of synovial membrane proliferation, enthesopathy, the slightest sensitivity was observed in the visualization of marginal bone erosions. At the same time, the markers of specificity were equally high.

2. In large joints, the proliferation of the synovial membrane was detected in a half of the joints and had predominantly high echogenicity, as well as accompanied by intraarticular overflow in all observations and may be considered an important marker for PsA. In small joints, synovial proliferation with predominantly low echogenicity occurred only in several numbers of the joints, due to their rarer lesion, and was combined with an increase in intraarticular fluid in majority of cases. The injury of the tendon-ligament apparatus in the PsA included enthesopathy in the knee joints, tenosynovitis in the ankle, radiocarpal joints and in the small joints of the hands and plants.
3. Ultrasound criteria as a marker of diagnosis of PsA were: the degree of severity of synovitis, as well as the presence of tenosynovitis and enthesitis. The strongest correlation was obtained between the activity of inflammation and vascularization of the synovial membrane (r = 0.591) and tenosynovitis (r = 0.547), as well as between the levels of ESR, CRP and leukocytes, the amount of inflammatory fluid (r = 0.401) and the degree of vascularization of the synovial membrane (r = 0.508).
4. The significant differences between PsA and RA were the presence of enthesopathies of the ligaments themselves of the patellar tendon and the quadriceps tendon of the femoral and the predominance of intraarticular overflow in small joints.

Abbreviations:

CRP – C-reactive protein; PsA – Psoriatic Arthritis; RA – Rheumatoid Arthritis; RF – Rheumatoid Factor; USG PD – UltraSonoGraphy Power-Doppler; MRI – Magnetic Resonance Imaging

Competing interests

None declared

Authors' contribution

Study conception and design: ER. Data acquisition: AS, LG. Analysis and interpretation of data: ER, AS, LG, MH, VS. Drafting of the manuscript: AS, MH, VS, ER. Significant manuscript review with significant intellectual involvement: ER. Approval of the „ready for print" version of the manuscript: ER, AS, LG, MH, VS.

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RESEARCH ARTICLE

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Characteristics of morphological changes in the skin of patients with allergodermatoses during long-term external application of fluorined steroids

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ABSTRACT

The article presents the results of studies of the effect of applying topical fluorinated glucocorticosteroids in combination with ceramides on the barrier function of the skin of experimental animals with allergic dermatoses (guinea pigs).

The purpose of the work: substantiation of the inclusion of ceramides in the base of topical fluorinated steroid preparations for the treatment of allergic dermatoses by studying the morphological changes in the skin of guinea pigs after the application of the indicated means of various compositions.

Materials and methods. Histological research was carried out on outbred guinea pigs of the same sex and condition (74 individuals). The animals were divided into separate groups depending on the applied drugs. The following combinations of drugs and, accordingly, guinea pigs were selected, which were divided as follows: IC – intact control (15 animals); O – base application (14); OC – base containing ceramides (15); FSt/kr – fluorinated steroids of strong action (betamethasone) (16); FStK/kr – fluorinated steroids of strong action (betamethasone) + ceramides (14).

Results. In order to study the traumatic effect of topical steroids on the skin and the possibility of preventing morphological (atrophic) disorders, an experimental study of the morphology of the skin of guinea pigs was carried out on a model of atrophy caused by long-term (14 days) application of topical fluorinated steroids of various compositions.

Applying the foundation to animals led to some thickening of the epidermal layer, while the morphology of the epidermis and the skin itself was not disturbed. The addition of ceramides led to the acceleration of proliferative processes and the development of proliferative acanthosis. Changes induced by betamethasone were noted mainly in the epidermis in the form of local atrophy of the epidermal layer. The addition of ceramides to a potent fluorinated steroid to some extent smoothed out the negative effects of the corticosteroid hormone. The average thickness of the epithelial layer increased by 2 times compared to the thickness of the epithelial layer of animals of the FSt/kr group and even slightly exceeded the indicators of intact animals. Vacuolar dystrophy of the cells of the spinous and granular layers occurred in all animals of the FStK/kr group. Lymphoid infiltration of the dermis, parakeratosis and acantholysis were not noted.

Conclusions. The results of an experimental study of the effect of topical fluorinated steroids of different composition on the skin of guinea pigs indicate the existence of differences between the drugs in terms of their degree of action on the intensity and development of pathological processes in experimental animals. A comparison of the effect on the skin of classic topical steroids and those additionally containing ceramides indicates the possibility of preventing the traumatic effect of hormones, which is especially important for patients with filaggrin gene mutations.

Keywords: allergic dermatoses, morphological changes, topical fluorinated steroids, ceramides.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript
Histological confirmation of the combined use effectiveness of fluorinated corticosteroids with ceramides.
The research hypothesis
the combined use of creams with ceramides and fluorinated corticosteroids in allergic dermatoses reduces the side effect of the skin barrier thinning.
The novelty added by manuscript to the already published scientific literature
The addition of ceramides to topical corticosteroid therapy prevents the traumatic effect of hormones, which is especially important for patients with filaggrin gene mutations.

Introduction

The modern pathogenetic model of atopic dermatitis (AD) can be represented as a chain, the links of which are considered: a set of predisposition genes, a reduced barrier function of the skin, a disorders of innate immunity, which are joined by external factors and characteristics of the adaptive immune response. The most significant genetically determined disorders in this disease are changes in the immune system and the skin barrier, the dysfunction of which is a favorable background for the development of AD [1, 2].

Most experts support the concept of AD development as a disease associated with abnormalities of the epidermal barrier [3, 4].

The increased activity of own proteases, which destroy structural components in the epidermis, and the presence of additional exogenous proteases produced, for example, by house dust mites or Staphylococcus aureus, facilitate the destruction of desmosomal contacts and the penetration of allergens into the skin. The functioning of the epidermal barrier is also affected by a disorder in the maturation and advancement of lamellar granules, which leads to a significant deficiency of acid, lipid, and enzyme components of the stratum corneum. AD-associated increase in the activity of sphingomyelin deacylase leads to a decrease in the production of ceramides [5, 6].

Damaged skin barrier is the most important factor in AD development, which is indirectly confirmed by the fact that the most characteristic places of localization of lesions in this disease are areas of the skin with a weakened epidermal barrier and increased protease activity [5, 6]. Constitutionally dry skin is also considered an essential feature, which is due to the reduced level of ceramides, squalene and free fatty acids in the stratum corneum lipids components of the natural moisturizing factor, the appearance of defects in intercellular lipid layers, increased transepidermal water loss [7].

Topical steroids, which are the main means of external treatment of patients with chronic dermatoses, depending on the dosage form and the strength of the corticosteroid, to one degree or another deepen atrophy, dryness, dehydration of the skin. The third generation of corticosteroids includes a large number of fluorinated glucocorticosteroids that have a strong and very strong local effect. These agents have more favorable properties of pharmacokinetics. At the same time, with long-term use of steroids, hypopigmentation, secondary infection, acne and striae, an increase in the level of cortisol in the blood, and aggravation of the course of osteoporosis are more common. Their development is due to the inhibition of fibroblast proliferation and collagen synthesis, as well as inhibition of the proliferative activity of keratinocytes and fibroblasts. In this regard, external remedies for AD patients, especially those with a filaggrin gene mutation, need appropriate correction to prevent the deepening of the morphological and functional changes inherent in this condition [8, 9]. The corresponding correction can be carried out by including ceramides in the base of the drug, which contribute to the restoration of the epidermal barrier due to the filling of lipids and are a conductor of active substances into the dermis [10].

The aim of the work was to justify the inclusion of ceramides in the base of topical fluorinated steroid drugs for the treatment of allergic dermatoses by studying the morphological changes in the skin of guinea pigs after applying the above-mentioned products of various compositions.

Materials and methods.

The study was conducted on outbred guinea pigs of the same sex and fatness (40 individuals). The animals were divided into separate groups depending on the applied drug. The animals were on a standard diet and received food that was equivalent in terms of qualitative and quantitative composition. The conditions of the animals were in accordance with the rules of the „European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes".

The possibility of correcting the complications of topical

steroid use (development of skin atrophy, increased xerosis, etc.) was studied in an experiment by introducing ceramides into the base of topical fluorinated steroids.

The following combinations of drugs and, accordingly, guinea pigs were selected, which were divided as follows: IC – intact control (15 animals); O – base application (14); OC – base containing ceramides (15); FSt/kr – fluorinated steroids of strong action (betamethasone) (16); FStK/kr – fluorinated steroids of strong action (betamethasone) + ceramides (14).

During the external examination, clinical changes were assessed on the excised areas of the skin, where samples were subsequently taken for histological examination. The samples were fixed in a 10% solution of neutral formalin, processed in alcohols of increasing concentration (for at least 3 weeks), embedded in celloidin paraffin. Sections with a thickness of 6–7 μm were stained with hematoxylin and eosin. The light-optical research was carried out under a Biolam R-12 microscope. The areas that were most typical for this experimental group were selected for the photos.

Statistical processing of the obtained results was carried out using a package of application programs for Microsoft Excel 2003. Analysis of qualitative data was carried out using the $\chi 2$ test. Average arithmetic values for a series of data (M) and errors of average values (m) were calculated. The reliability of the obtained data was assessed by pairwise comparison and determination of the confidence interval based on the calculation of the Student coefficient (t). Differences were considered statistically significant at $p<0.05$ [11].

Results and discussion

In order to study the traumatic effect of topical steroids on the skin and the possibility of preventing morphological (atrophic) skin disorders by varying the components of an external agent: both the active substance (corticosteroid) and components that reduce their harmful effect (ceramides), an experimental study of the morphology of the skin of guinea pigs was carried out on a model of atrophy caused by long-term (14 days) application of topical fluorinated steroids of various compositions.

When examining all micropreparations of the IC group, a clear division into the epidermis and the skin itself, which had a normal structure, was revealed. In the multilayered epidermis, all the transitions from viable dividing cells to those that were keratinized took place. The basal layer consisted more often of vertically elongated keratinocytes with dark nuclei, the outlines of which were clear, mitoses were few. The spinous layer had several rows (4–6) of sufficiently densely arranged polygonal cells. As a rule, intercellular contacts were clearly visible. The epidermocytes of the granular layer (3–4 rows) are polymorphic, containing a large number of keratohyalin granules in the cytoplasm, from dispersed in the lower rows to large sharply basophilic closer to the stratum corneum. The thickness of the stratum corneum was uniform throughout the section. Its compact layer tightly adhered to the surface of the epidermal layer, loose, moderately desquamated from its surface. The cellular elements of different layers of the dermis are typical, all obligate derivatives are present, the vessels of the microcirculatory channel had a normal structure. Endothelial cells contained flat, sharply basophilic nuclei. The blood vessel filling was moderate (Fig. 1), the width of the epidermis on average for the group was 15.3 u.o.

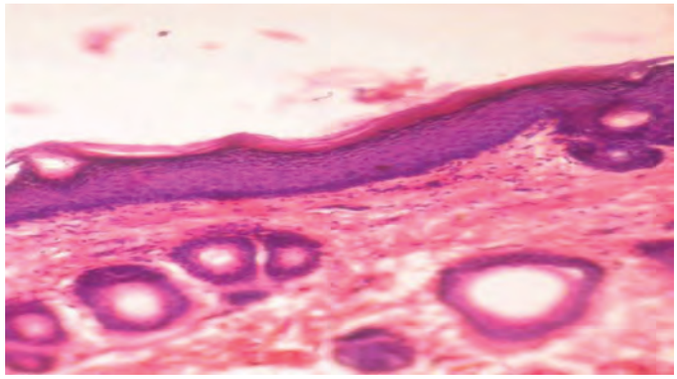


Fig 1. The skin of an intact guinea pig. Normal histology of epidermis and dermis. Hematoxylin and eosin, x 150

The thickness of the epidermal layer of guinea pigs of the studied groups is shown in the table 1.

Table 1. The thickness of the epidermal layer of guinea pigs (u.o.)

Group	The thickness of the epidermal layer
IC, n = 15	15,3 ± 0,91
O, n = 14	20,75 ± 1,78
OC, n = 15	34,71 ± 3,07*†
FSt/kr, n = 16	10,25 ± 0,81*
FStK/kr, n = 14	20,14 ± 1,47†

Note. * – significantly differs in relation to IC ($p < 0,05$); † – is significantly different in relation to a similar drug that does not contain ceramides ($p < 0,05$).

Applying the foundation to animals led to some thickening of the epidermal layer, the morphology of the epidermis and the skin itself was not disturbed at the same time. Thickening occurred due to an increase in the number of rows of the spinous layer (up to 8-9 rows), the exfoliation of the stratum corneum increased (Fig. 2a). The addition of ceramides led to the acceleration of proliferative processes and the development of proliferative acanthosis (Fig. 2b). Mitotically dividing cells were found more often than in intact animals (Fig. 3), increased epidermopoiesis led to a pronounced thickening of the epidermal layer due to the spiny layer, which was significantly thickened (up to 15-16 rows). In some areas, the epidermis formed acanthous outgrowths that penetrated the dermis, and there were horn cysts. On average, the thickness of the epidermal layer in the group exceeded the control indicators by 67% (Table 1). Dystrophic and degenerative phenomena were not observed.

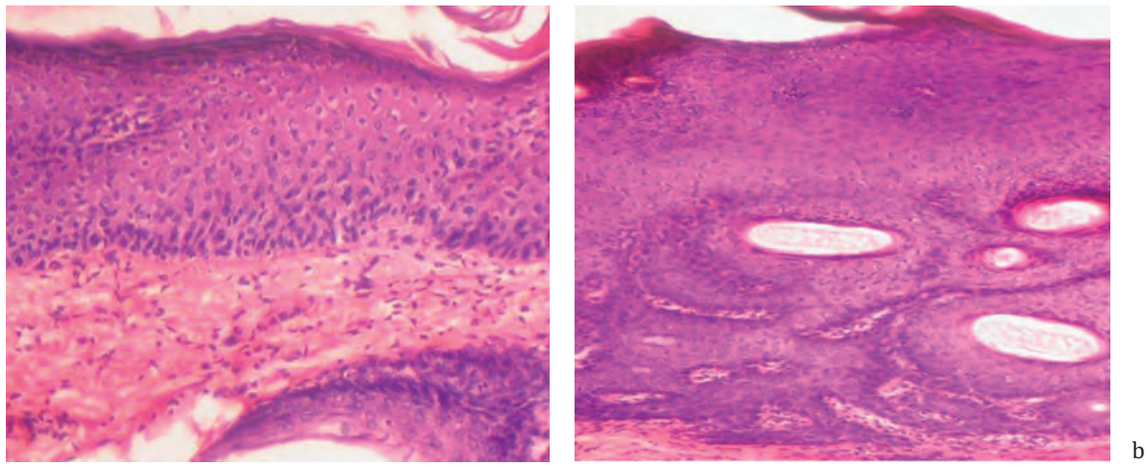
a  b

Fig. 2. Guinea pig skin.
Thickened epidermis of normal morphostructure, O group (a). Strongly thickened epidermis, acanthous outgrowths, OC group (b). Hematoxylin and eosin, x 150

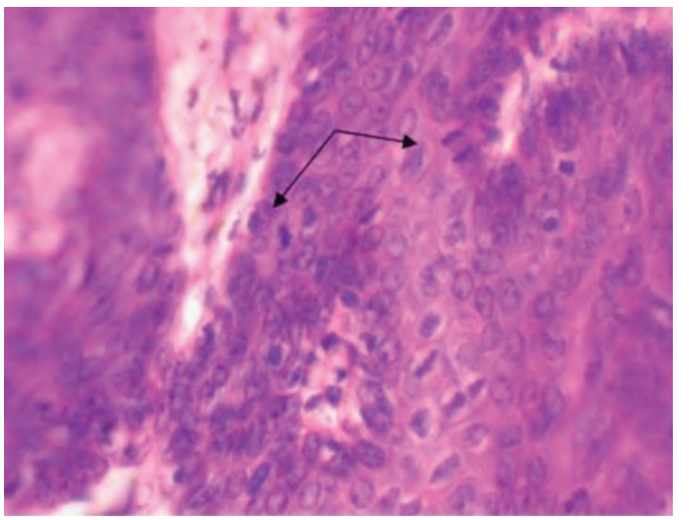


Fig. 3. Guinea pig skin, OC group.
Numerous mitoses of basal layer cells (arrows). Hematoxylin and eosin, x 150

Changes induced by betamethasone (group FSt/kr), were observed mainly in the epidermis. First of all, local atrophy of the epidermal layer should be noted. Thinning was uneven, mostly interfollicular (located between two hair follicles) areas of the skin were altered (Fig. 4a), although occasionally there was atrophied epidermis located above the follicles (Fig. 4b).

On average, the thickness of the epidermal layer was reduced by a third compared to the control group (Table 1). If we measure the thickness of the epithelial layer only in places of thinning, it was 6.17 u.o, which is only 40% of the control values. Atrophic epidermis contained from 3 to 6 rows of keratinocytes.

As is known, the development of atrophy is preceded by an edematous-inflammatory stage, the signs of which were found in the skin of animals of this group. Pronounced swellings were noted in the papillary layer of the dermis (Fig. 4a). Fluid from the dermis penetrated the epidermis, expanding and breaking intercellular connections and forming spongy bubbles (Fig. 5).

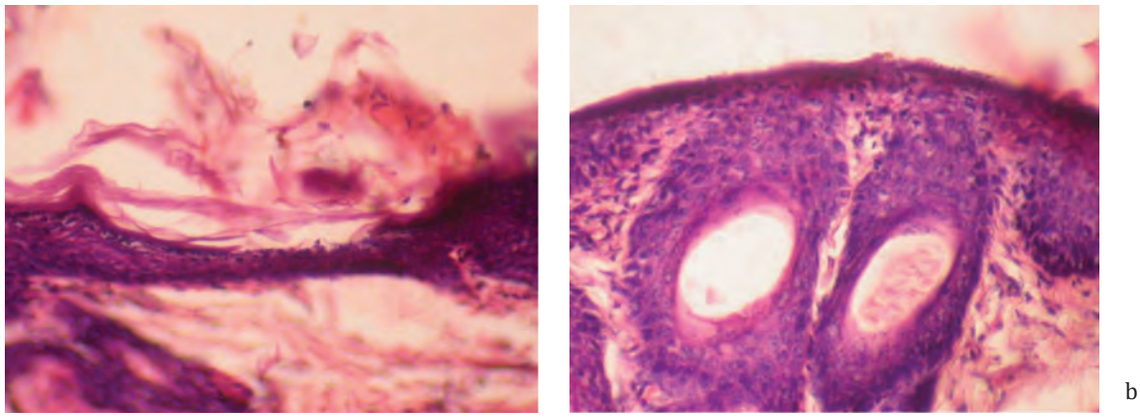
a  b

Fig. 4. Guinea pig skin, FSt/kr group.
Thinned epidermal layer of the interfollicular area, swelling of the papillary layer of the dermis (a). Atrophy of the epidermis above the hair follicles (b). Hematoxylin and eosin, x 150

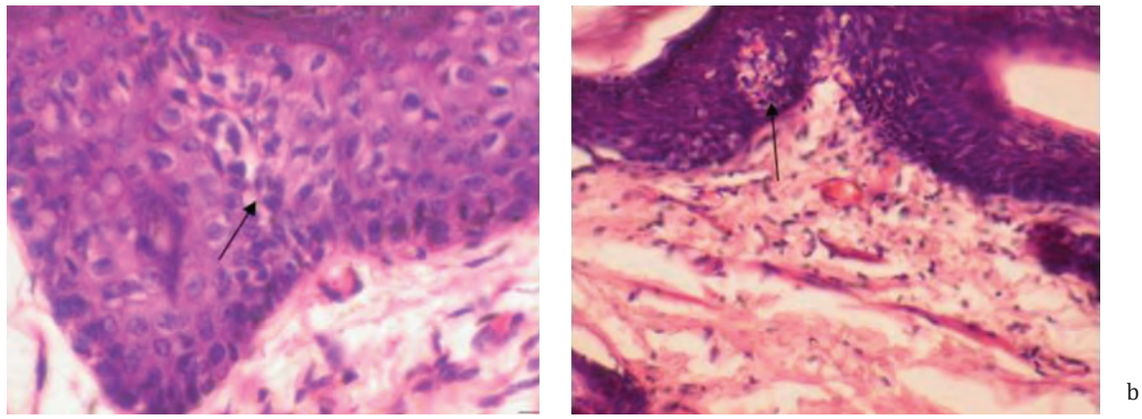


Fig. 5. Guinea pig skin, FSt/kr group.
Penetration of fluid from the dermis into the epidermis (arrow) (a), x 200. A spongy bubble in the epidermis (arrow) (b), x 150. Hematoxylin and eosin

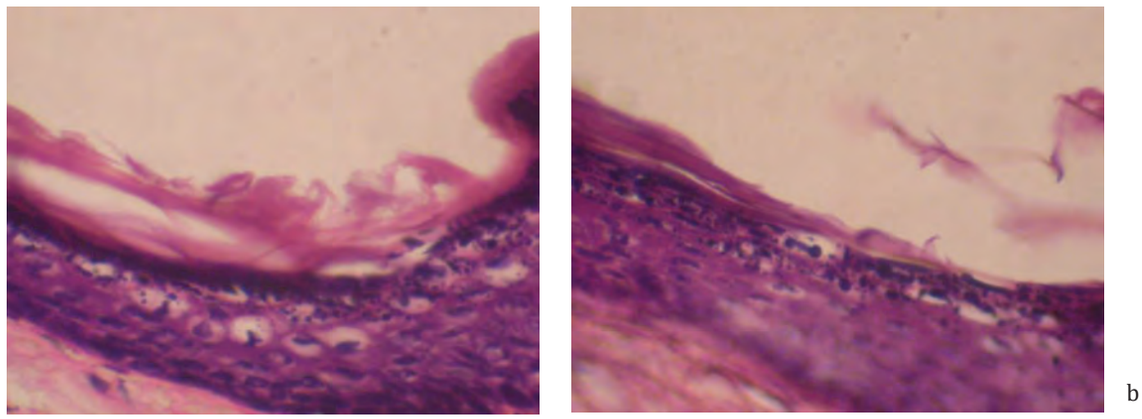


Fig. 6. Guinea pig skin, FSt/kr group.
Vacuolar dystrophy of cells of spinous and granular layers (a, b). Hematoxylin and eosin, x 200

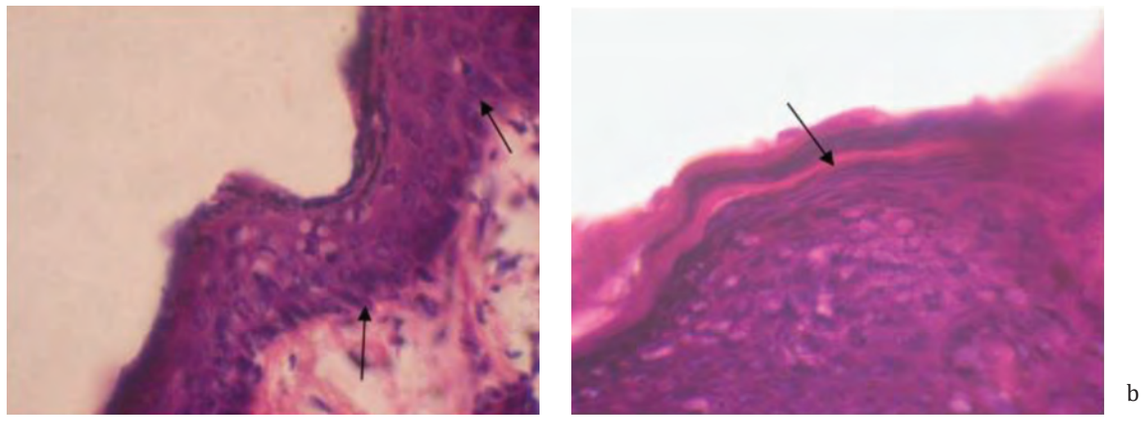


Fig. 7. Guinea pig skin, FSt/kr group.
Acantholysis of spinous layer cells (arrows), intracellular edema (a). A parakeratic cell, nuclei in the stratum corneum (arrow), absence of a granular layer, thickening of the spinous (b). Hematoxylin and eosin, x 150

In parallel, dystrophic manifestations developed - intense intracellular swelling of keratinocytes of the spinous and granular layers was noted (Fig. 6).

Vacuoles were located perinuclearly, and in more pronounced cases occupied the entire cytoplasm, shifting the nucleus to the periphery and making it flatter. Damage to keratinocytes and loss of intercellular connections led to acantholysis. Acantholytic spherical cells with oxyphilic cytoplasm were located, as it were, separately from the surrounding cells and were found along the entire length of the epidermis (Figure 7).

The process of keratinization was also disturbed: there were many intraepidermal horn cysts filled with horn masses, and rare foci of parakeratosis were also identified. The stratum corneum cells in the parakeratic cells appeared immature because they contained rod-shaped, horizontally oriented nuclei (Fig. 7b). The stratum corneum outside the foci of parakeratosis is usually partially or completely exfoliated. The granular layer between the skin layer is expressed unevenly, under areas of parakeratosis, as a rule, it is absent, the spiky layer is thickened. The stratum corneum, which contained an excess of keratin, was also determined in hair follicles (Fig. 8a). Cellular infiltration of the papillary layer of the dermis was enhanced, lymphocytes predominated in the infiltrate (Fig. 8b). The blood supply of the vessels of the dermis was reduced.

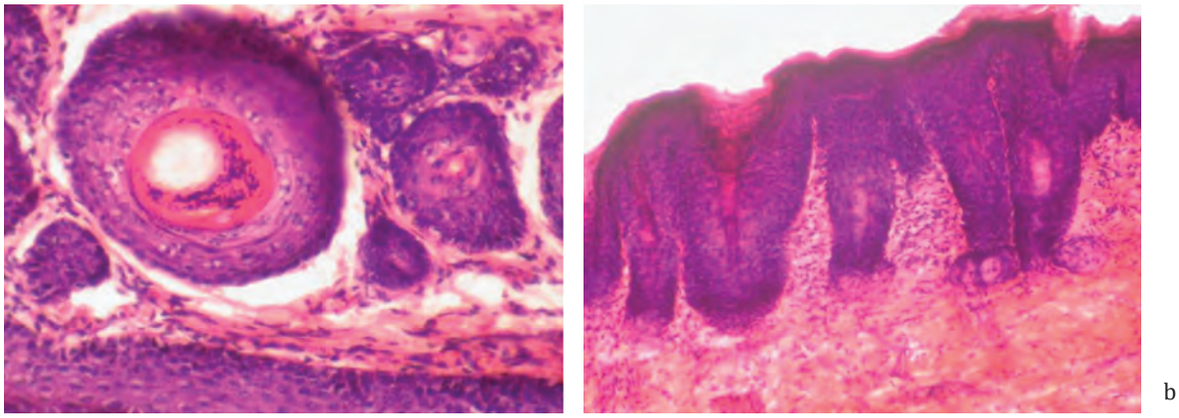


Fig. 8. Guinea pig skin, FSt/kr group.
Keratin in the stratum corneum of the hair follicle (a). Acanthosis, increased lymphoid infiltration of the dermis (b). Hematoxylin and eosin, x 150

The addition of ceramides to a potent fluorinated steroid to some extent smoothed out the negative effects of the corticosteroid hormone. The average thickness of the epithelial layer increased by 2 times compared to the thickness of the epithelial layer of animals of the FSt/kr group and even slightly exceeded the indicators of intact animals (Table 1). It should be noted the unevenness of the epidermis: areas of normal thickness alternated with thin (rarely) or thickened ones (Figure 9a). Mitoses in the basal layer were more frequent than in the previous group. Acanthosis was the result of the formation of long epithelial outgrowths that deeply penetrated the dermis. In response to the elongation of the epidermal appendages, the dermis reacted with swelling hypertrophy of papillae that penetrated deeply into the epidermis and elongation of capillaries, that is, papillomatosis (Fig. 9b).

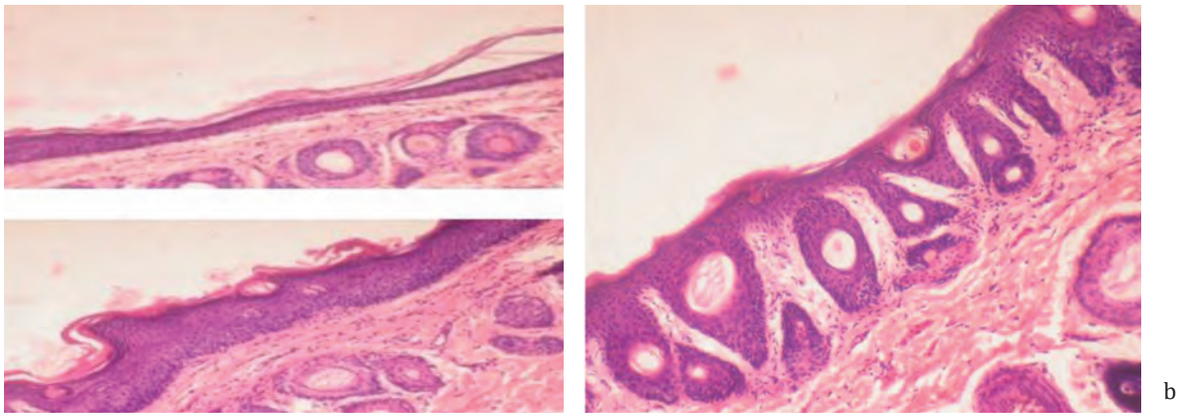


Fig. 9. Guinea pig skin, FStK/kr group.
Areas with thinned (above) and normal (below) epidermis (a). Acanthosis and papillomatosis, swelling of the papillary layer of the dermis (b). Hematoxylin and eosin, x 150

Vacuolar dystrophy of cells of spinous and granular layers was found in practically all animals (FIg. 10). Lymphoid infiltration of the dermis, parakeratosis and acantholysis were not noted.

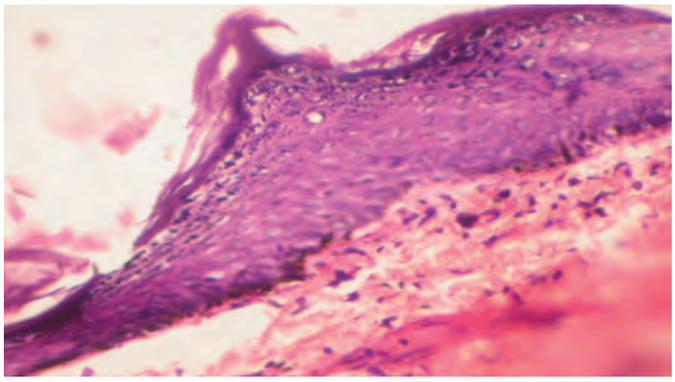


Fig. 10. Guinea pig skin, FStK/kr group.
Vacuolar dystrophy of cells of spinous and granular layers.
Hematoxylin and eosin, x 200

Thus, the investigated fluorinated corticosteroid (betamethasone) led to the development of skin atrophy in experimental animals, the epidermis of which was thinned by 33% compared to the IC group).

Thinning of the skin in all animals occurred due to the thinning of the epidermal layer, and not the skin itself. Atrophy was accompanied by the development of dystrophic processes of a non-specific nature both in the epidermis and in the dermis.

Ceramides, when added to the studied drugs, had a selective effect: the more significant the atrophy induced by corticosteroids, the more noticeably ceramides enhanced the proliferation of keratinocytes and the stronger the epidermis thickened not only relative to the positive ((by 96%), but also IC (by 32%). If the thinning was insignificant, then the effect of adding ceramides was not so indicative.

As for the application of the base, to which the skin of animals reacts by thickening, ceramides potentiate this property of the base and cause further significant thickening of the epidermis. Ceramides also significantly reduce the manifestations of inflammatory and dystrophic processes in the skin.

Thus, for the external treatment of chronic dermatoses in patients with a mutation of the filaggrin gene, that is, before treatment, they already have skin changes characteristic of these conditions (atrophy, dryness, dehydration, desquamation, etc.), it is advisable to use topical steroids with the addition of ceramides. The development of this class of drugs will prevent side effects that are caused or exacerbated by topical steroids.

Conclusions

The inclusion of ceramides in a topical fluorinated corticosteroid (betamethasone) prevented the traumatic effect of hormones by increasing the proliferation of keratinocytes and thickening the epidermis. The use of these means will prevent the occurrence or aggravation of side effects.

Competing interests

None declared.

Ethical statement

This study was carried out in accordance with the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific* Purposes and approved by the Institutional Ethics Committee.

Authors' contributions

All the authors have contributed equally at the results presentation in the paper.

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RESEARCH ARTICLE

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Lateral sinus floor elevation with simultaneous mucosal cysts management

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ABSTRACT

Introduction. Specialists in the field often face uncertainty in deciding whether to perform sinus lifting surgery in the presence of a mucosal cyst during the pre-implantation preparation of patients with maxillary sinus pathology. While some specialists believe that the sinus lifting operation cannot be performed in the presence of sinus pathology and should be resorted to after a long period of healing, others believe that it can be performed in the presence of sinus pathology or simultaneously with sinus sanitation. As a result, there are more controversies about the treatment tactics, stages, and timing required to achieve the rehabilitation of these patients, demonstrating the significance of the problem at hand.

Materials and methods. The study included twenty patients who were referred to the Department of OMF Surgery and Oral Implantology "Arsenie Guțan" and the dental clinic "OmniDent" between 20.06.2016 and 01.01.2019 for implant-prosthetic rehabilitation due to partial edentulism in the upper jaw in the lateral area and the presence of a mucosal cyst in the maxillary sinus. The first group comprised of seven patients in whom the mucosal cyst was completely removed while simultaneously undergoing lateral sinus lifting. The second group consisted of five patients, aged between 18 and 67 years (average 45 years), who underwent marsupialization of the mucosal cyst. The third group comprised of six patients in whom the cyst content was only aspirated, without removal or marsupialization of the cyst.

Results. All three methods were found to be effective, although total perforations of the sinus mucosa were recorded in the first two groups, preventing the performance of sinus lifting at that stage. The method of aspirating the cystic content, however, is a simple and low-risk procedure that does not carry the risk of perforating the sinus membrane and provides predictable results.

Conclusions. The mucosal cyst does not present a contraindication to sinus lifting but requires additional surgical procedures.

Keywords: sinus lifting, mucosal cyst, pseudocyst, mucocele, retention cyst, implant rehabilitation.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

The management of mucosal cysts during preimplantation assessment and the optimal approach for rehabilitating affected patients remain highly controversial, highlighting the pressing need for further research on this issue.

The research hypothesis

Maxillary sinus mucosal cysts do not necessarily contraindicate sinus lifting procedures.

The novelty added by the manuscript to the already published scientific literature

A comparative study of the currently known main methods was carried out. The advantages and disadvantages of each method were determined.

Introduction

Implant-prosthetic rehabilitation has become the preferred method for treating patients with various forms of edentulism. In the lateral areas of the upper jaw, a deficiency in the height of the alveolar ridge is often encountered, resulting from the pneumatization of the maxillary sinus and the atrophy of the alveolar process following tooth loss. The low subantral bone height creates challenges for the insertion of endosseous dental implants. Currently, the most used methods for solving this issue are transcrestal or lateral sinus lifting operations.

The lateral sinus lift technique involves creating a bony window on the lateral wall of the maxillary sinus, elevating the Schneiderian membrane, and grafting the subantral space with a variety of materials, including autogenous bone, allografts, xenografts, alloplastic materials, or mixtures thereof [1-3]. Despite the fact that this procedure alters the anatomy of the maxillary sinuses by lifting the sinus membrane, it has been demonstrated not to have any adverse impact on sinus function.

Non-pathological sinus augmentation poses little risk of ostium obstruction or sinus dysfunction due to the cranial position of the ostium. However, when bone augmentation of the maxillary sinus is performed in the presence of a pathological condition that significantly reduces the lumen of the sinus, the risk of obstruction after a sinus lift can be increased. This scenario can result in the stagnation of mucus secretion inside the sinus, leading to a sinus infection [4-6].

A small mucosal cyst in the maxillary sinus (MSMC) does not pose a contraindication to the sinus lift procedure, as the risk of complications during or after surgery, such as membrane perforation or ostial obstruction, is minimal [7-9].

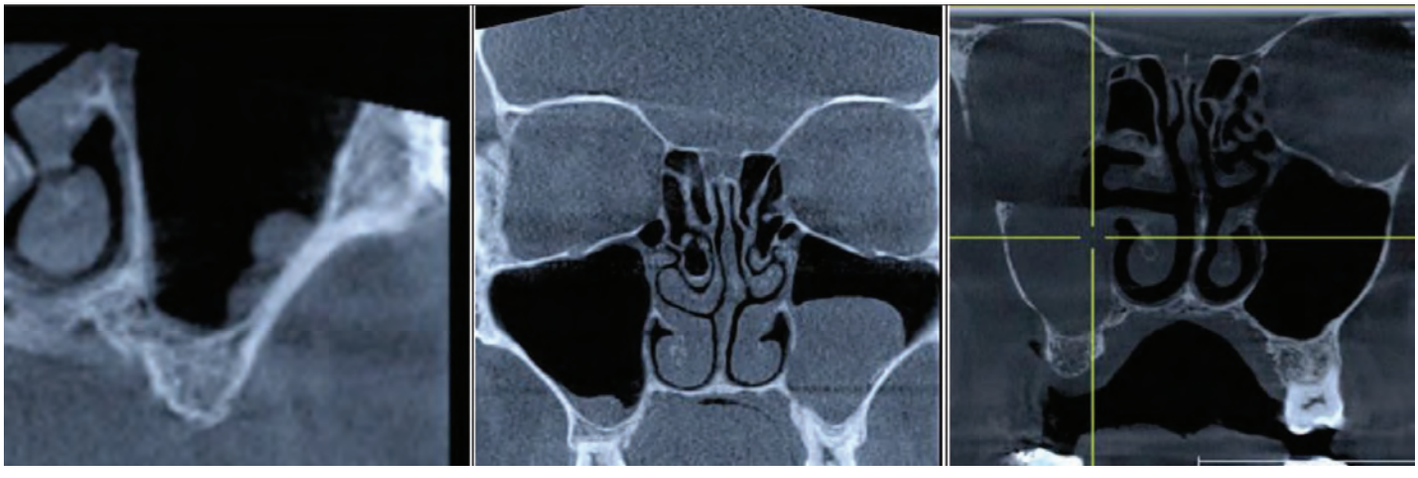
Nevertheless, the presence of a large MSMC (occupying at least one-third of the sinus volume) can create difficulties during the elevation of the sinus membrane and may damage the ostium following the augmentation procedure [5, 10].

Obstruction of the ostium can lead to mucus accumulation inside the maxillary sinus and loss of sinus ventilation [4-6]. The severe complications that can occur are caused by the spread of the infection to other paranasal sinuses, the orbit, and even the cranial cavity [11, 12].

The formation of retention cysts (secretory type) (Fig. 1a) is believed by Gerlings P. and Lindsay J. to be caused by blockage of the excretory duct of the seromucous glands due to sinus infection, allergy, odontogenic infection, or traumatic extraction [13, 14].

Mucosal pseudocysts of the non-secretory type (Fig. 1b), as described by Harar R., are formed by the accumulation of exudate in the conjunctival layer of the maxillary sinus mucosa, between the periosteum and the epithelial layer. The occurrence of pseudocysts is a topic of debate. Some authors argue that in 50% of cases, the etiology is odontogenic due to the penetration of oral microflora in the cystic fluid (bacteriologically determined in the cystic fluid), as well as the fact that most cysts originate from the mucosa of the sinus floor at the level of the apical odontogenic foci of the affected teeth [15]. Bacterial toxins destroy the walls of the capillaries, leading to protein loss in the tissues. This results in an increase in the osmotic pressure and blockage of the reabsorption of tissue fluids. As a consequence, fluid accumulates in many areas of the subepithelial space, which ultimately coalesce to form the pseudocyst [14].

Mucocele (Fig. 1c) is a lesion that is most found in the frontal sinus, less often in the ethmoid cells, and sporadically in the maxillary sinus. Kuczkowski J. performed the most extensive characterization of mucoceles and described them as cyst-like formations [3]. The mucocele is lined with epithelium, contains mucoid fluid, and has an expansive, destructive growth that is associated with obstruction of the natural ostium of the respective sinus. The mucocele causes compressive resorption of the bone through intraluminal fluid pressure, resulting in invagination into adjacent cavities such as the cranial box, orbit, or under the skin surface. Clinical symptoms of mucocele include headache, diplopia, decreased vision, and nasal obstruction. Histologically, the mucocele exhibits sac-shaped hernias of the sinus mucosa [16].



a b c

Fig. 1 Radiological appearance of mucosal cysts
(a) – retention cyst, (b) – pseudocyst, (c) – mucocele

Mucocele in the maxillary sinus is a relatively uncommon condition, with most cases reported in Japan, where they are referred to as postoperative cysts [17]. Among the 22 cases of antral mucocele reported by Kuczkowski J. [3], all 22 were caused by the Caldwell-Luc radical cure. Similarly, all 71 cases reported by Kaneshiro et al. in Japan were secondary, occurring after radical cure of the sinus [18].

In the pre-implantation preparation of patients with maxillary sinus pathology, specialists are often faced with uncertainty when deciding whether to perform sinus lifting surgery in the presence of a mucosal cyst. Some specialists believe that sinus lifting cannot be performed in the presence of sinus pathology and should be delayed until a later stage of healing, while others believe that it can be done in conjunction with sinus drainage. As a result, there is considerable controversy regarding treatment tactics, stages, and optimal timing for achieving rehabilitation in these patients, highlighting the relevance of the problem at hand.

Materials and methods

The study included twenty patients who sought implant-prosthetic rehabilitation for partial edentulism in the lateral area of the upper jaw and the presence of a mucosal cyst in the maxillary sinus at the Department of OMF Surgery and Oral Implantology "Arsenie Guţan" and the dental clinic "OmniDent" between 20.06.2016 and 01.01 2019. All patients underwent a sinus lift operation despite the presence of the MSMC. Depending on the method of managing the mucosal cyst, patients were divided into three study groups.

The study was approved by the Ethics Committee (EC) of the *Nicolae Testemiţanu* State University of Medicine and Pharmacy, decision No. 77 (17.06.2016). The chair of the EC was Nacu Viorel.

The first study group consisted of seven patients, aged between 31 and 64 years (with an average age of 43 years). In this group, the mucosal cyst was completely removed, and a lateral sinus lifting operation was performed simultaneously. The cyst removal was carried out using two methods: endoscopic removal and removal through a small perforation of the mucosa in the lateral wall of the maxillary sinus.

The endoscopic method involved the following steps: First, the uncinate process was identified through anterior rhinoscopy of the respective nostril using a straight rigid optic (0°), and subsequently resected. Next, angled optics (40°) were used to identify the natural ostium of the maxillary sinus, which was slightly enlarged with the aid of Blacksley forceps. The cyst was then completely removed from the maxillary sinus through the natural ostium using antral forceps. Following cyst removal, sinus lifting was performed using the classical method, as illustrated in Fig. 2.

The second method used to completely remove the cyst involved the following steps, as illustrated in Fig. 3: First, a trapezoidal incision was made in the edentulous area of the oral mucosa. The muco-periosteal flap was then detached, and an osteotomy of the side wall of the maxillary sinus was performed using drill no. 5 from the "Dentium" kit, taking care not to damage the sinus mucosa. Next, the maxillary sinus was punctured using a needle and syringe through Sch-

Table 1. Patients' data included in the study.

Nr.	Sex	Age, year	Sinus left/ right	Group	Preoperative mucosal thickness, mm	Postoperative mucosal thickness, mm	Sinus lifting Immediate/delayed
1	m	52	r	2	28.83	19.77	delayed
2	w	50	l	2	37.99	12.35	immediate
3	w	64	r	1	36.20	0	delayed
4	m	64	r	3	25.94	28.47	immediate
5	m	57	l	2	16.44	16	immediate
6	w	67	r	2	22	4.87	immediate
7	m	38	r	2	24	3.23	immediate
8	w	39	l	1	28	0	immediate
9	m	34	r	3	12.68	12.68	immediate
10	m	18	r	1	17.13	0	delayed
11	w	61	r	3	14.22	13.05	immediate
12	m	49	r	2	23.44	3.55	immediate
13	m	46	l	3	20.28	20.28	immediate
14	m	47	l	3	18.34	0	immediate
15	w	57	r	1	32.56	0	immediate
16	m	55	l	2	17.14	8.1	immediate
17	w	31	l	1	29.33	0	immediate
18	m	55	r	1	15.29	0	immediate
19	m	46	l	2	37.77	9.6	immediate
20	m	40	l	3	15.64	14.66	immediate
Total	m – 13 w – 7	min – 18 max – 64 average – 48.33	r – 11 l – 9	1 2 3	min – 12.68 max – 37.99 average – 23.81	min – 0 max – 28.47 average – 8.33	i – 17 d – 3

Note: Descriptive statistics; m – man; w – woman; l – left; r – right; i – immediate; d – delayed

neider's membrane, and the cystic contents were aspirated. With the help of a thin forceps and suction, the cystic membrane was carefully pulled through the microperforation created by the needle, exposed in the oral cavity, and removed. After cyst removal, the sinus mucosa was elevated, and the perforation was closed using either PRF membranes or artificial membranes. Finally, the subantral space was augmented, with or without the insertion of implants (Table 1).

Group 2 included five patients aged between 18 and 67 years (with an average age of 45 years) who underwent marsupialization of a mucosal cyst. The intervention method was similar to the previous one in terms of surgical steps. The only difference was that the cyst membrane was sectioned with scissors without being entirely removed (Fig. 4).

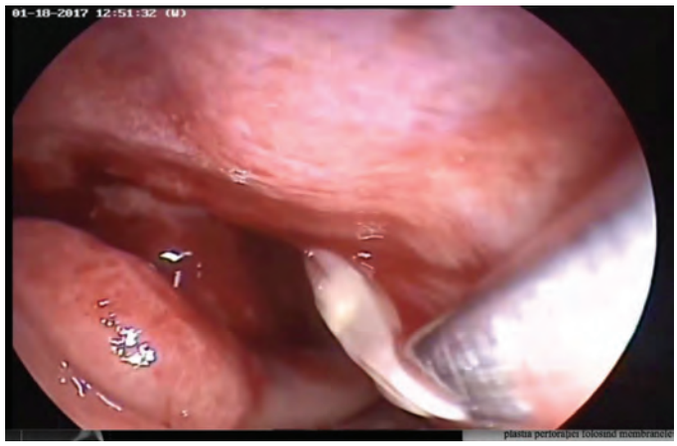
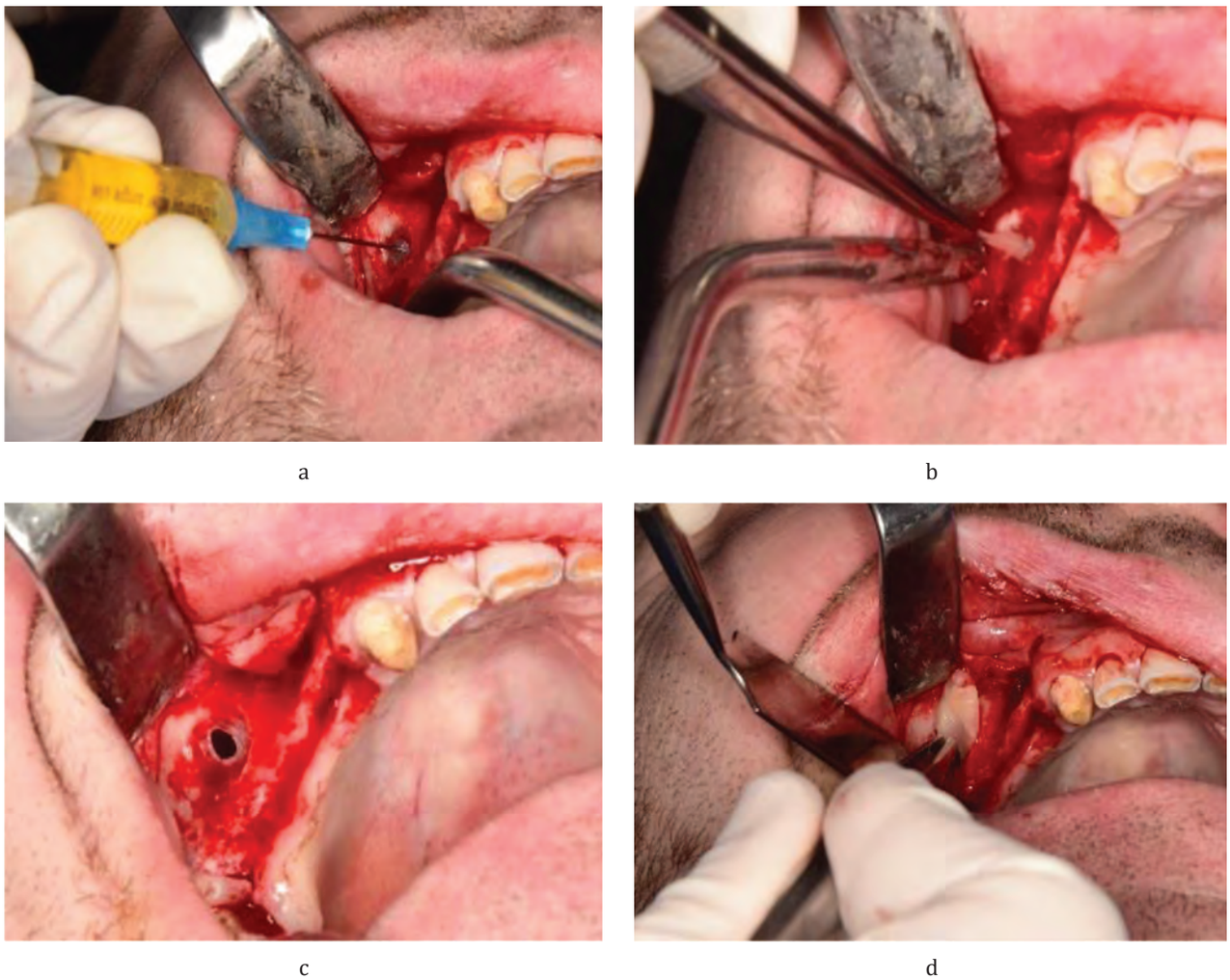


Fig. 2 Endoscopically assisted removal of the cyst through the middle meatus



a b c d

Fig. 3 Removal of the cyst with simultaneous sinus floor elevation
(a) – aspiration of the cystic content, (b) – removal of the cystic membrane, (c) – perforation of the sinus membrane, (d) – perforation closure with a PRF membrane

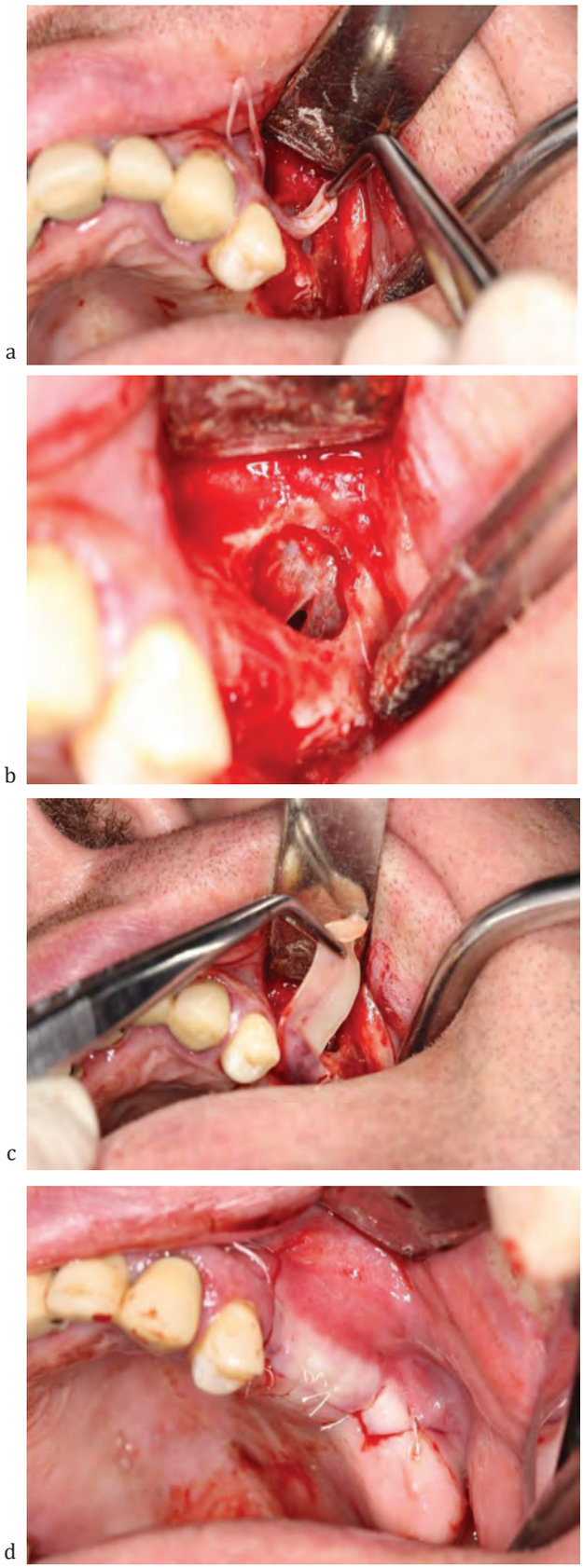


Fig. 4 Stages of maxillary cyst marsupialization
(a) – removal of the portion of the cystic membrane, (b) – sinus membrane perforation, (c) – perforation closure with a PRF membrane, (d) – wound closure

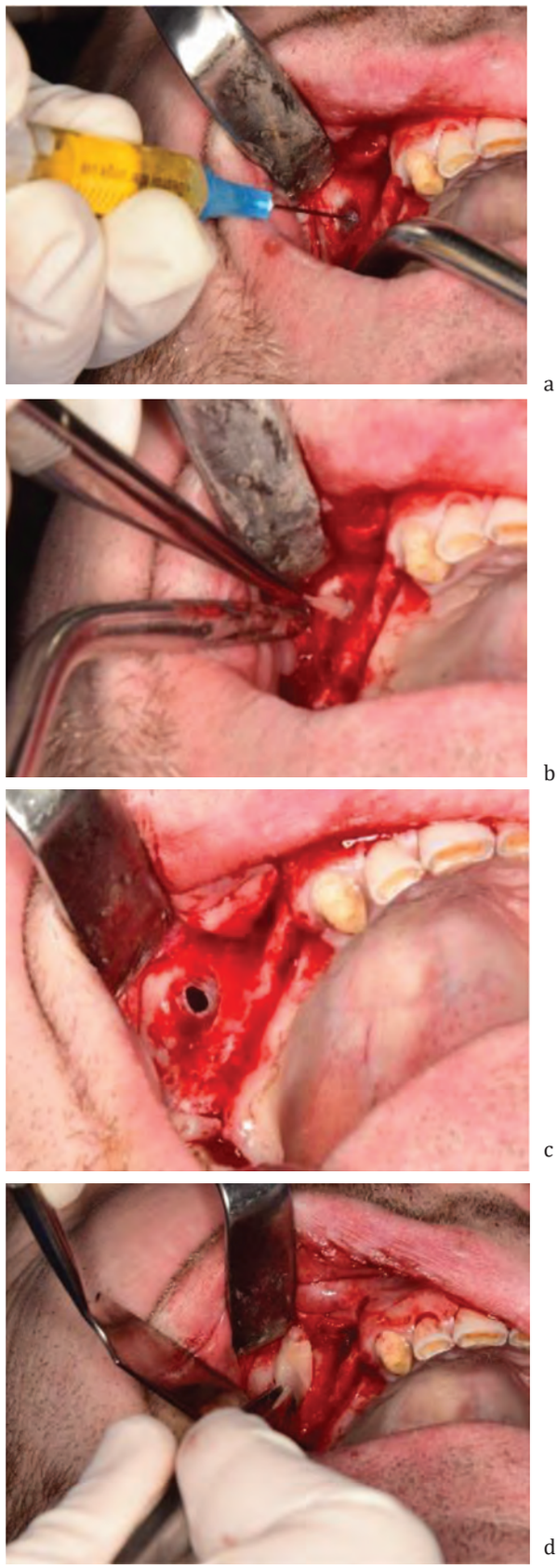


Fig. 5 Stages of sinus lifting with aspiration of the cystic content
(a) – osteotomy of the lateral wall, (b) – aspiration of the cystic content, (c) – elevation of the sinus membrane and augmentation of the subantral space, (d) – simultaneous insertion of endosseous dental implants

Group 3 comprised six patients aged between 34 and 61 years (mean age: 53 years). In these patients, only the cyst content was aspirated, without removal or marsupialization of the cyst (Fig. 5).

A computed tomography was performed on all patients both before and after the operation, with a minimum interval of 6 months between the two scans. The Lund-Kennedy scale was assessed before and after the operation (Fig. 6).

Fig. 6 Schematic representation of the Lund-Kennedy scale
(0) – full pneumatization, (1) – thickening of the mucosa up to 5 mm, (2) – thickening of the mucosa up to 1/3 of the sinus volume, (3) – thickening of the mucosa up to 2/3 of the sinus volume, (4) – lack of sinus pneumatization

Results

Of the patients in our study, the majority were men (13 out of 20, or 65%). The average age of the patients was 48 years. We assessed each patient's Lund-Kennedy scale both before sinus floor elevation and 6 months after the operation.

Based on the tables presented, it is apparent that the first group of patients, in which the cyst was completely removed, had no recurrences. In the second group, where marsupialization of the cyst was performed, the cyst visibly decreased in volume during the postoperative period. However, in the third group, where only the cyst content was aspirated, the cyst returned to its original size after a short period of time. While these results suggest that complete removal of the cyst is the most effective method for treating mucosal cysts when the sole goal is to remove the cyst, it remains unclear which method is optimal when a sinus lifting operation is also necessary. Specifically, it is unclear whether the method used in Group 1 remains the most effective in this context.

Discussions

Lin Y., et al. [9] described a two-stage protocol with delayed sinus lift, in which sinus grafting was performed approximately 3 months after pseudocyst removal. Eleven patients were treated using this approach. During the first operation, a small lateral access was made to remove the pseudocyst. Three months later, sinus augmentation was performed, and dental implants were inserted 6 months after the sinus grafting procedure. The authors reported no instances of sinus membrane perforation during sinus membrane elevation, no implant loss, and no cystic recurrence after a mean follow-up of 29 months. One of the disadvantages mentioned was that patients had to undergo two separate surgeries. Furthermore, the procedures and elevation of the sinus floor were performed through the same access route as in the first surgical intervention. This required dissection between the sinus membrane and the oral mucoperiosteum, which increased the technical difficulty of the sinus lifting operation.

We believe that this method should only be considered when other approaches have failed. In fact, we have used this technique in only two cases (one from group 1 and one from group 2) when attempts to remove or marsupialize the cyst resulted in large perforations, making it difficult to predict the outcome of the sinus lift. Therefore, we decided to postpone the sinus lift for 3 months. The procedure was successfully performed without any perforations or risks of pushing the augmentation material into the sinus.

The one-step protocol was first introduced by Pikos et al. In this approach, a conventional bone "window" is created, and then the pseudocyst is removed by intentionally perforating the sinus membrane. Sinus grafting is performed after the sinus membrane is closed with resorbable collagen membranes. Although the authors reported positive results, it is important to note that these outcomes are based on individual cases. Furthermore, intentional perforation of the sinus membrane is contrary to the biological principles of the sinus augmentation technique [1]. While it is possible to close the perforation with collagen membranes, complications such as contamination of the graft material and its dispersion in the maxillary sinus may occur [1, 11].

We used the given method to treat the first group of patients. Although this method allows to remove the cyst entirely, we found that it resulted in an unpredictable-sized perforation instead. After the removal of the cyst and the elevation of the sinus floor, we had to perform the closure of the perforation. In our study, we performed PRF membrane closure. However, in one case, we couldn't continue the intervention due to a massive perforation. Considering that mucosal cysts of the maxillary sinus do not require specific treatment (surgical or medicinal), are not considered tumors, and do not typically lead to complications, it may not be necessary to remove the cyst in its entirety, which could result in intraoperative complications.

Table 2. Obtained results

			Cyst management		
			Removal	Marsupi-alization	Aspira-tion
Age, years	minimum		18	31	34
	maximum		64	61	64
	average		47	45	53
	standard deviation		18	10	10
	25th percentile		47	39	46
	median		49	43	55
	75th percentile		58	51	61
Sex	m	total	5	5	4
		column N %	100.0	62.5	57.1
		lower 95,0%	-	29.5	23.5
		upper 95,0%	-	88.1	86.1
	w	total	0	3	3
		column N %	0.0	37.5	42.9
		lower 95,0%	-	11.9	13.9
		upper 95,0%	-	70.5	76.5
Lund-Kennedy before surgery	2	total	3	3	4
		column N %	60.0	37.5	57.1
		lower 95,0%	20.9	11.9	23.5
		upper 95,0%	90.6	70.5	86.1
	3	total	1	3	1
		column N %	20.0	37.5	14.3
		lower 95,0%	2.3	11.9	1.6
		upper 95,0%	62.9	70.5	50.1
	4	total	1	2	2
		column N %	20.0	25.0	28.6
		lower 95,0%	2.3	5.6	6.5
		upper 95,0%	62.9	59.2	64.8
Lund-Kennedy after surgery	0	total	3	3	3
		column N %	60.0	37.5	42.9
		lower 95,0%	20.9	11.9	13.9
		upper 95,0%	90.6	70.5	76.5
	1	total	1	2	0
		column N %	20.0	25.0	0.0
		lower 95,0%	2.3	5.6	.
		upper 95,0%	62.9	59.2	.
	2	total	0	3	4
		column N %	0.0	37.5	57.1
		lower 95,0%	-	11.9	23.5
		upper 95,0%	-	70.5	86.1
	4	total	1	0	0
		column N %	20.0	0.0	0.0
		lower 95,0%	2.3	-	-
		upper 95,0%	62.9	-	-

Note: Descriptive statistics; lower 95% and upper 95% represent a 95% confidence interval

In our search for new treatment methods, we decided to apply the marsupialization technique, which we commonly used for managing massive odontogenic cysts, to treat these patients. This technique involves ensuring the drainage of the cyst over an extended period, which reduces the intracystic pressure and causes the cyst to shrink in volume. However, in contrast to jaw cysts, where the cystic membrane attaches to the bone walls, this is not possible with sinus cysts. As a result, the mucosal cyst tends to recur, first shrinking in volume and then growing again.

The authors used the given method to treat eight patients and observed the following advantages:

- the method enables directed perforation in most cases;
- it reduces pressure on the augmentation material during the healing period.

However, the biggest disadvantage of the method is that intentional perforation can enlarge the perforation if the membrane is thin. In one case, we had to postpone the sinus lift due to a large perforation.

Maiorana C., et al. proposed an alternative technique for treating sinus cysts [19]. Their method involved creating access to the maxillary sinus through osteotomy and aspirating the cystic fluid using a fine needle inserted through the sinus membrane. This step reduced both the pseudocystic volume and the tension on the sinus membrane. With these factors minimized, the sinus lift technique could be completed with minimal risk of ostium obstruction and sinus membrane perforation.

We used the given method to treat seven patients and found that unlike the first two groups, all cases resulted in good outcomes without complications. The method has several advantages, including its simplicity and ease of performance, non-perforation of the mucosa, and reduction of intracystic pressure, which facilitates detachment of the mucosa. However, the main disadvantage is that aspiration of only the liquid does not allow for complete enucleation of the pseudocyst.

Felisati G. proposed a protocol that combines the intraoral approach with the transnasal endoscopic sinus approach in a single surgical session [5]. This approach allows for transnasal treatment of pseudocysts and rhinosinusitis (if present), which is a relative contraindication to the sinus lift technique. Specifically, the elevation of the floor of the maxillary sinuses is performed through an intraoral approach immediately after the endoscopic surgery.

This protocol is an ideal solution for sinus grafting in patients with pseudocysts and nasopharyngeal conditions, such as multiple sinus cysts, nasal septum deviation, *agger nasi* cell hypertrophy, and concha bullosa, that can affect sinus ventilation. However, when treating only a pseudocyst that can be removed through a simple intraoral approach, the protocol has certain limitations. These include the need for two distinct surgical teams (ENT surgeons and OMF surgeons), treatment under general anesthesia, and a significant increase in price, operative time, and postoperative morbidity.

It is important to note that there is no universal method for managing mucosal cysts of the maxillary sinus in candidates for sinus lifting, and each case must be approached individually. Unfortunately, this problem has been insufficiently addressed in the specialized literature, and further studies are needed with larger patient groups to better understand and address this issue.

Conclusions

1. The mucosal cyst does not present a contraindication to sinus lifting but requires additional surgical procedures.
2. All methods have their advantages and disadvantages; there is no optimal method.
3. The sinus lifting method with the removal of the cystic membrane through a small perforation is effective. However, sometimes it creates large perforations, which require additional plastic surgery, increase the cost of the intervention, and increase the risks of postoperative complications, although the cyst does not recur.
4. The sinus lifting method with marsupialization of the cyst does not create large perforations. However, the cyst may recur but in a smaller size. This results in less pressure on the augmentation during the healing period. Nevertheless, it is important to close the perforation and monitor the patient's progress over time.
5. We consider the sinus lifting method with aspiration of the cyst content to be the most effective because it does not create perforations, it is easy, and the postoperative period has low risks.

Competing interests

None declared.

Authors' contributions

Conception and design of study – DS, AM; Data collection – AM, ID; Analysis and/or interpretation of data – AM, AMo; Drafting the manuscript – AM, DS, ID; Revising the manuscript critically for important intellectual content – AM, DS, AMo; Approval of the final version of the manuscript – all authors.

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REVIEW ARTICLE

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Benign prostatic hyperplasia - etiology, clinical features and management. Historical and contemporary aspects

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ABSTRACT

Introduction. Benign prostatic hyperplasia and chronic prostatitis are the most common conditions in men, the frequency of which varies with age. Chronic prostatitis (infectious or inflammatory) has a frequency of 8-35% in patients aged 20-50 years, reaching a maximum of 60-70% in those aged over 50 years.

Materials and methods. Materials for the study served the medical literature regarding benign prostatic hyperplasia and chronic inflammation, published in the local and international scientific journals. Scientific databases like *Cochrane Library, Medline, Scopus, Medicus, NCBI, PubMed, Google Scholar* were used to find the necessary articles. Research methods – analysis, synthesis, systematization, and description.

Results. After analyzing the available data, a review of the literature was conducted which highlighted both the strong and weak points of the historical medical approaches to addressing benign prostatic hyperplasia, as well as the ontogenetics and anatomical characteristics of the prostate gland. This included examining the incidence rates, concepts of causation and development, principles of diagnosis and classification of benign prostatic hyperplasia. The review also revealed the pros and cons of using mini-invasive treatment strategies versus traditional transvesical approaches in treating this condition, as well as the ongoing and significant socioeconomic impact in underdeveloped countries.

Conclusions. There remains the issue of reducing intra- and post-operative complications after benign prostatic hyperplasia surgery, especially a voluminous one, which imposes itself as a very critical problem in the development of an effective treatment strategy. For the first time, a problem was described by assessing the particularities of some biochemical criteria at local surgical site and in blood serum, histological - at the level of nodular prostatic hyperplasia and at the border of the surgical site. This requires a complex correlational study to assess the biochemical, histological and immunohistochemical parameters, including the evaluation of the associations or coexistence of benign prostatic hyperplasia and chronic prostatitis.

Keywords: urology, benign prostatic hyperplasia, prostatitis, etiology, morphogenesis, treatment, advantages and disadvantages.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

In order to develop an effective medical and surgical approach for reducing the risk of complications during and after the removal of a large benign prostate gland growth, known as nodular hyperplasia, it is crucial to have a thorough understanding.

The research hypothesis

There is needed an effective treatment approach that can decrease

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postoperative complications and improve monitoring of general hemostasis and inflammation at the surgical site.

The novelty added by manuscript to the already published scientific literature

A systematic study of the specialized literature was carried out, in order to highlight the etiological, clinical and diagnostic features and the impact to obtain an effective hemostasis after enucleation of benign prostate nodular hyperplasia and define criteria for local surgical site monitoring in reducing the postoperative complications. Due to limited data, there is a need for a comprehensive examination using biochemical, histological, and immunohistochemical methods. This includes evaluating the potential relationship or simultaneous occurrence of both benign prostatic hyperplasia and chronic prostatitis.

Introduction

The prostate is a small gland with an anatomically important role and is part of the male reproductive system. Various changes in the prostate cause serious problems with the lower urinary tract. Among the most common prostate pathologies that induce micturition disorders, has an impact on the quality of life, starts from the working age, but with a major impact in old age, are benign prostatic hyperplasia (BPH), chronic prostatitis (PCr) and prostate carcinoma (CP). However, the most important is BPH [1-4].

Benign prostatic hyperplasia and chronic prostatitis are the most common conditions in men, the frequency of which varies with age. Chronic prostatitis (infectious or inflammatory) has a frequency of 8-35% in patients aged 20-50 years, reaching a maximum of 60-70% in those aged over 50 years. BPH has a significant frequency after the age of 50-60 years with a maximum of 76.3-81.4% in the elderly population (75-90 years) [3, 5]. In the last 2-3 decades, BPH became a modern problem due to affecting younger population (35-40 years), being placed fourth after arteriosclerosis, hypertension and diabetes, having a significant social-economic impact, the etiology being still enigmatic and questionable [3, 6-8].

In the literature there are various opinions on the etiology of BPH, which are determined by the totality of the diseases characteristic of this organ (atrophy, inflammation, hyperplasia and neoplasia) which are contradictory despite the fact that they have the same pathogenetic substrate [1, 9-11].

Advances in diagnostic technologies, pharmacological and surgical treatment in recent years have greatly contributed to the optimization of diagnosis and treatment by mini-invasive surgical resolution of obstructive syndrome in BPH [6, 12, 13]. However, the individualized approach to treatment allows to achieve the optimal result of treatment and improve postoperative quality of life [4, 12, 14]. The optimization of treatment in BPH and the reduction of the intraoperative and postoperative complication risks remains open, being an ongoing problem, which requires further research.

The purpose of the study is to review and analyze medical literature on the aspects of etiology, clinical picture, diagnosis, treatment, and social-economic impact of BPH, in order to determine the optimal tactics and the risks of intra- and postoperative complications especially in voluminous BPH.

Materials and methods

Materials for the study served the medical literature of various lengths – monographic, scientific, randomized, and non-randomized clinical trials, reports of clinical cases and case series, national and international guidelines about BPH and chronic prostatitis published in the national and international journals. The articles were searched using the following databases – *Cochrane Library, Medline, Scopus, Medicus, NCBI, PubMed, Google Scholar*. In parallel, a literature search was performed to identify meta-analysis, randomized controlled trial and reviews articles related to „benign prostate hyperplasia", „prostatitis", „etiology", „morphogenesis", „adenomatous hyperplasia", „adenomectomy" in the PubMed, MEDLINE, ISI Web of Science, Cochrane databases. There were selected only the most relevant and recent articles. Research methods - analysis, synthesis, systematization, and description.

Ninety-one primary sources that were relevant were chosen based on their impact score, and the selection criteria included a scientific, reproducible, and transparent approach to the subject under discussion, as well as subsequent data extraction and analysis. To ensure varied conclusions, the research findings from foreign studies were supplemented by published research data from the Republic of Moldova. A narrative synthesis of the data was performed as part of the qualitative research process.

Results and discussions

As a result of the literature analysis, there were selected 91 articles scientifically important. Based on the analyzed data, the synthesis of literature revealed the aspects of historical, medical approaches to the problem of BPH, ontogenetic and topographical aspects of the prostate; incidence

and concepts of etiology and morphogenesis, diagnosis and classification principles of BPH, and especially on advantages and disadvantages of different treatment strategies in BPH, from classical to mini-invasive methods as well as the socio-economic impact of BPH.

Historical approaches to benign prostatic hyperplasia. BPH, a term widely used in recent decades, is a benign hypertrophic-hyperplastic benign pathological formation, known in the past as „prostatic hypertrophy", „adenomatous hyperplasia", „chronic lobular prostatitis", „benign nodular hypertrophy", „adenoma of the paraurethral glands" and/or „prostate adeno-fibro-leiomyomatic". For the first time, Goldberg V. (1960) introduced the term of prostate adenoma, and the surgery to treat the nodular tumor – adenomectomy, a notion successfully used until the last decade [7, 15, 16]. Based on the fact that prostate adenoma implies both, BPH and a nodular hypertrophic-hyperplastic process, the Consensus Conference on Benign Prostate Hyperplasia (Monaco, 1995) established the final term to be BPH [17].

Over decades, research has been carried out to determine the etiology and pathological processes that induce hyperplasia of the prostate, invoking various factors, such as: pelvic venous stasis, aging, atherosclerosis and vascular atheromatosis, hormonal theory (androgens, estrogens), oxidoreductase, hormonal disbalance – mediated hormonal feedback etc. [18]. The role of infection and chronic inflammation as a predictive factor of hypertrophy in the prostate was proposed by Tsekhanovskii G. (1901). Later Vertkin I. (1931) provided results that proved the infectious-inflammatory role as controversial and proved that inflammation is a consequence of nodular hyperplasia (cited by Aivazean A, 1957) [19]. However, McNeal (1968) reported a 44% incidence of prostate inflammation in BPH based on autopsy findings in older men, while the role of chronic inflammation has been supported by many other researchers in the following decades [20, 21]. However, the infectious-inflammatory role as a predictive factor as well as the cause of prostate inflammation has remained a subject of heated debate for a significant period [22].

Over decades, the hormonal theory has been reinforced as an important etiological factor in the evolution of BPH. The theory was described by exposed by Dunaevskii L. (1935), Topchanov A. (1949) and many others (quoted by Aivazean A, 1957). Dunaevskii L. marks the role of testicular hyperfunction in prostatic hypertrophy, associated with advanced age, which induces hyperplasia of the periurethral glands with the formation of nodular hyperplasia [19]. Peterman N. (1939) states that in prostatic hypertrophy the prostatic parenchyma evolves to hyperplasia and adenomatosis, and it is impossible to distinguish the origin of the periurethral glands from the prostate glands, while the remaining tissue after adenomectomy is nothing but the residual peripheral area of the prostate [23].

Another important issue of BPH from a historical perspective is about the treatment, conservative and surgical. The first stage includes the use of various bimanual methods, therapeutic procedures that declined with the emergence in the 20th century of α-adrenergic antagonists, the 5-alpha reductase inhibitor, phytotherapeutic preparations, which are recognized as one of the most effective therapeutic treatments and relieve the symptoms of the lower urinary tract (LUTS) [24-26].

Surgical prostatectomy was first introduced by Eugene Fuller (1895) according to some sources. Fuller's approach was associated with a considerable mortality rate of approximately 18%, and as a result, it faced several objections. Later, the technique was improved and adopted in 1900 by Peter Freyer, who despite a 5% mortality rate had a great success [27, 28].

A remarkable advance in BPH surgery is considered the elaboration of the technique of retropubic extravesal "prostatectomy" conceived by Terrence Milin (1945), which achieved significant reduction of mortality [29]. In this context, Aivazean A. (1957), mentions the significance of radical andenomectomy in BPH introduced by Russian surgeons: Podrez F. (1887) – adenomectomy by suprapubic approach, Druzhinin M. (1889) – by perineal approach, Fedorov S. (1899) performed transvesical scraping of the prostate, Kholtsev B. (1906) – two-step adenomectomy by transvesical approach, Lidinskii A. (1922) – by extravesical retropubic approach [19].

The beginning of a true revolution in the surgical treatment of BPH is considered the first transurethral resection surgery performed by Maximilian Stern and Joseph McCarthy (1932) using a wire loop under visual control, this being an instrument developed by the authors that later became the precursor of the current resectoscopy – TURP (transurethral resection of the prostate) [29].

Also, BPH surgery in recent decades has benefited from mini invasive surgical techniques such as: transurethral vaporization – TUVP being an alternative to TURP/TUIP; Laser enucleation: Nd:YAG, KTP:YAG, with diode, Holmium: YAG; HoLEP; Cryosurgery - bipolar electrocoagulation, intermittent coagulation resection, rotoresection. A dynamic evaluation study 5 years after the application of HoLEP and open transvesical prostatectomy established a promising evolution with the need for follow-up surgeries at a low rate [4, 30-32]. However, for prostates with nodules larger than 80-100 g, TURP had a rate of re-surgery rate of 55% and mortality rates of 6% [33, 34]. In this context, Novikov I., et al. (2001), Shakhmachev V. (2010) emphasize that mini-invasive treatment is promising, but still requires confirmation in large clinical trials, because the remaining tissue fragments after coagulation not always can be easily handled, and urinary infections or secondary interventions in connection with complications, as well as some in the result of long-term hospitalizations have made these methods less preferable [35].

Ontogenetic aspects, topographic and zonal anatomy of the prostate. Morphologically, the prostate consists of a glandular and fibro-muscular component, surrounded by a capsule. Prostate growth manifestations occur throughout life, much faster in the puberty period. At the age of 15-16 years, the division into acinar or alveolar structures with ep-

ithelial-papilliform cellular projections takes place, with the formation of glandular prostatic parenchyma and opening of the ducts [36]. Structural differentiation of the prostate is considered when the glandular epithelium manifests secretory characteristics, with basal, neuroendocrine cells and immunoreactivity maximum values of secretion reaching at 20-21 years. With the differentiation and organization of the prostate parenchyma occurs the maturation of glandular secretory cells. During this period, the secretory cells become mature expressing the secretory form of both the acid phosphatase isoenzyme (ALK-P) and the prostate-specific antigen (PAS) [37, 38].

From the puberty period, the prostate enlarges 10 times in volume, reaching maximum functionality at the age of 30-45 years, and then gradually atrophies. From the age of 45-60 years, atrophy of glandular tissue occurs. With age, both atrophy and prostatic hyperplasia can occur, which can be correlated with the androgenic hormonal status, otherwise nodular hyperplasia of the prostate (BPH) can occur, with significant frequencies at the age of 61-75 years [39].

From an anatomical-topographic point of view with improvement of imaging techniques and regarding surgical topography, 4 surfaces of the prostate have been described – anterior, posterior and two inferior-lateral, a base projected upwards to the bottom of the urocyst and a lower-facing apex, which has a fibro-muscular casing that externally envelops the prostate through the sphincter of the urethra, and inside it, urethra is surrounded by the urocystic sphincter. Outside the external sphincter, we can distinguish the periprostatic capsule, which originates from the visceral pelvic fascia, while in the inside the fibro-muscular layer can be identified. The fibro-muscular layer is a real capsule of the prostate. Towards the centripetal prostatic parenchyma from the internal surface of the fibro-muscular capsule are divided septa that compete in a central area being crossed by the ejaculatory ducts and the prostate utricle, the urethra being located anterior [20, 39].

The anatomical-functional features of the prostate are also dependent on the anatomy of the neuro-vascular system, the architectonic-functional being stacked in the plexus: related and efferent, superficial (at the capsule level) and profound (septa, glandular-muscular structures). Arterial blood originates from the lower urocystic arteries (*a. visceralis inferior*), the middle rectal arteries (a*. rectalis media*) and internal pudendal arteries [40].

Of significant importance for the surgical diagnostic and interventional orientation are the knowledge of the anatomical-topographic landmarks of the prostate based on the studies carried out by McNeal J. (1968-1978) and Sampaio F. (1992) which divided the prostate into areas. Anatomically quantifying with clinical importance 4 distinct areas at the level of the prostate: frontal, peripheral, central and transition area [20, 41]. Of the most important in the clinical-diagnostic and surgical perspective is the peripheral and transition area.

According to some biopsy studies, the transition zone in 70% is the site of BPH and only in about 10-20% of malignant neoplasms. In hyperplastic processes, including in BPH, the central and partially peripheral areas are considerably compressed, becoming a thin layer with the appearance of a surgical pseudocapsule after enucleation of nodules in BPH [42, 43]. However, the central area, which includes about 20% of the prostate volume, is less susceptible to inflammatory processes and can be the site of about 5% to 10% of accidentally detected malignant tumors. This area may play an important role in the development of BPH [36, 44].

The zonal division of prostate has a valuable practical and predictive importance due to the knowledge of the risk of preferential distribution and the prostate structural contribution in the evolution of specific lesions such as prostatitis, BPH, and prostate carcinomatous neoplasia [36, 43].

The incidence and concepts of etiology and morphogenesis of BPH. Equal prevalence of BPH between European and African countries is noted in the literature. However, if talking about disease progression, authors Handisuriya A., et al. (2001) noticed a more severe course of BPH in the African population. The incidence of statistical prostate adenoma also varies from country to country due to both the lack of data as well as overlap of clinical picture with other nodular processes such as fibroid – 11.3%, myoma – 0.3%, fibromiomyoma – 1.2% [45, 46].

The etiology of BPH at the current stage remains incompletely elucidated and contradictory. Such an opinion is also determined by the totality of diseases characteristic of this organ such as infections, inflammation, hyperplasia, and neoplasia that often counter or have the same etiopathogenetic factors [10, 11].

Currently, the following etiopathogenetic factors of BPH are old age, excesses or sexual abstinence, liver cirrhosis, but also some life-style habits such as smoking, alcoholism, obesity, hyperglycemia and diabetes. The key role according to most experts is hormonal disorders (androgens and estrogens) associated with aging [47].

The effect of androgens in BPH is mediated by cellular interaction, based on androgen receptors (ARs) by stimulating stromal and epithelial cell growth with intensified epithelial-mesenchymal transition [48]. According to Nickel J. (2008), the primary role in the evolution of BPH is due to estrogens more than due to androgens, which would explain the incidence of nodular hyperplasia in the transitional area on the one hand and on the other hand by converting testosterone into estrogen under the action of aromatase [49]. According to studies by Peehl D., et al. (1998) and Coppe J. (2010) in 50% of men who underwent adenomectomy up to the age of 60 years old and in 9% after 60 years old, genetics has a predictive role [50, 51].

An important role is given to oxidative stress. The role of free radicals such as RLO, OPL, and SAO in the pathogenic mechanisms of prostate adenoma evolution has been described. The evolution of prostate adenoma may be an alternative pathway of prostate carcinogenesis due to disorders of prostate growth promoted by oxidative stress and inflammatory mediators [52]. Majority of experts state that

aging, significant imbalance of the free radicals, infections and inflammation are recognized as predictive factors of BPH and prostate cancer [11].

Therefore, it is worth mentioning that androgens, estrogens, disorders of epithelial-cellular interactions, growth factors, neuroreceptors and infections can play a pathogenetic role in prostatic tissue hyperplastic processes and induce the formation of a chronic heterogeneous prostatitis underlying BPH morphogenesis [53].

BPH morphogenesis evolves through two main stages. The first stage is the proliferative process of fibromuscular stroma, which includes important changes in fibroblasts, capillaries, fibromuscular stroma, and the composition of glycosaminoglycan that induce the formation of primordial stromal nodule (NSP) or more commonly called early nodules. In about 70% of cases, nodules in the transition zone can be found [54, 55].

According to structural morphological changes, NSPs are divided into immature mesenchymal nodules (NMIm), fibroblastic stromal nodule (NSFB), fibromuscular stromal nodules (NSFM) and muscular stromal nodules (NSM). Under the interaction between cellular-stromal and acinar-epithelial relationship, proliferation of glandular structures occurs, thus forming the proliferative center. In the second stage, when the nodules are growing with advancing age, the stromal component in the nodules is reduced quantitatively. Simultaneously with the proliferation of the adjacent nodule, other proliferative outbreaks occur. It should be noted that the incidence of histopathological changes in BPH precedes clinical symptoms [43]

Diagnosis and principles of classification of prostate adenoma. The clinical and diagnostic features of prostate pathology are viewed from three etiopathogenetic directions: infectious-inflammatory (prostatitis), BPH and prostate cancer. Prostate cancer (PC), a diagnosis that is based on clinical symptoms, paraclinical, imaging, histology, and cytopathology. The most common conditions are prostatitis and BPH and both pathologies represent a reactive and symptomatic pattern of the lower urinary tract requiring a diagnosis of prevention and control [56].

Depending on the clinical disorders in BPH, they are divided into irritative and obstructive manifestations. In the course of the disease, three stages have been identified: the prostatism – or compensatory stage, the incomplete retention stage without dystonia of the urocyst and the incomplete retention stage with dystonia of the urocyst [17].

From the point of view of clinical symptoms, BPH is manifested by symptoms of the lower urinary tract (LUTS), and prostatitis with predilection of pain syndrome and painful ejaculatory dysfunction. Some comparative studies show that painful ejaculation may be present in 5–31% in men with AP-driven LUTS [57, 58]. Currently both pathologies benefit from modern sophisticated diagnosis and treatment, which is based on national and international guidelines. Chronic prostatitis in medical history can be an early sign in the development of BPH [59, 60].

BPH is a nodular process with dimensions between 27–50 mm^3 and/or greater than 80 mm^3. Prostate adenoma has a clinical picture of lower urinary tract symptoms (LUTS) associated with benign enlargement of the prostate (BPR) leading to bladder outlet obstruction (BoO) which is assessed by quantifying the international score of symptoms caused by prostate adenoma (IPSS) as well as assessing the quality-of-life index (QoL) [3, 13, 60].

The diagnosis of BPH is based on history, rectal digital exam, laboratory investigations, imaging methods such as intravenous urography, cysto-urethrography, ultrasound (USG), computed tomography (CT), magnetic resonance imaging (MRI), uroflowmetry, international prostate symptom score (IPSS), prostate-specific antigen (PSA), hemostasis and rheological features of the blood serum, renography, cystoscopy, BPH biopsy [60, 61].

Determination of PSA levels according to some studies in BPH is welcomed. Bhat A. mentions that the persistence of PSA after prostatectomy is a warning signal for the doctor [62]. However, in this context, a correlation study of the PSA level in the blood serum and the histological peculiarities is welcomed.

The dimensions of the nodules in BPH correlate with the weight, which frequently reaches the dimensions of an apricot (50-100 g.), but much more voluminous forms have been described, up to 250-400 g. With reference to the dynamism of the annual progress of BPH, according to some studies in recent years it has an evolution of about 0.6 mm per year. Depending on size, BPH is divided into small nodular hyperplasia ≤25-30 mm^3, medium nodular hyperplasia – 30-80 mm^3, large nodular hyperplasia ≥80 mm^3, giant nodular hyperplasia >250 mm^3.

Depending on the configuration, BPH can evolve in aspect of spherical solitary node, or in the form of two to three nodules and in shape of grape. Taking into account the nature of the growth, the following forms have been described: BPH intraurocystic (intravesical), preurocystic (retrotrigonal), suburocystic (intraticgonial) and mixed nodular form due to the presence of a diffuse growth [60].

Aleksandrov V. (2007) describes five stages of morphogenesis of BPH [46]:

- Stage I – formation of immature adenoma consisting of 2-3 reinforced acinar structures;
- Stage II – quantitative enlargement of the glandular structures that form proliferative centers;
- Stage III – emergence in peripheral areas of new proliferative centers/outbreaks;
- Stage IV – retention of secretion of the acini of proliferative centers with cystic dilation;
- Stage V – all acini forming proliferative centers or most of them are cystic dilated with epithelium atrophy.

Histological examinations have shown that the presence of inflammatory processes has an etiopathogenetically predictive role and is significant for the postoperative period [63]. Epithelial-muscular nodules in BPH are frequently associated with chronic inflammatory processes [64]. Kohnen P. et al. (1979) reported an inflammatory process prevalence of 98% in 162 examined cases, Kramer G. (2006) states that

chronic inflammation is frequently present in BPH, predilection in lumpy nodular BPH, with higher PSA levels and a higher risk of acute urinary retention [65-67].

Currently, BPH, especially the voluminous form, is a contemporary problem, due to both high incidence and prevalence, its evolution and serious complications that is associated with, as well as due to the shortcomings of pharmacological and surgical techniques used by modern medicine [3, 14].

Surgical treatment strategies in prostate adenoma, advantages, and disadvantages. For many years, managing BPH has had its pros and cons as efforts have been made to refine non-invasive treatments, surgical interventions, and adenomectomy hemostasis techniques. Komlev D.L (2004) notes that the surgical procedure in treating BPH, a major share 75.7% belongs to the transurethral adenomectomy (TUR) compared to the open transvesical method – 24.3% [69]. It is remarkable that due to the technological potential from the last decades, the medical and surgical management in BPH has improved and the patients' outcome has improved [68, 69].

Today, the gold standard is transurethral endoscopic method (TUR) [29, 32], which is performed in many countries, including for BPH ≥80 mm^3. Similar opinions can be found in the local literature [31, 70]. However, we must mention that in lumpy nodular BPH, open adenomectomy interventions are preferred, partly due to the difficulty of making a long resection, but also due to the high risk of larger postoperative complications.

Notwithstanding that endoscopic, transurethral resection of the prostate (TUR-P) in BPH is considered "gold standard", medical practice demonstrates that in voluminous nodule BPH the surgical treatment remains a valid option to this day. In this regard, Lopatkin N. et al. (2009), Martov A. et al. (2006), state that approximately 7-30% of surgical maneuvers for the treatment of BPH are performed with open surgery, with preferred surgical techniques described by Fedorov-Freyer [17, 71]. In addition, a good part of foreign authors from high-income countries mention the advantageous clinical efficiency of open transverse approaches compared to the TUR in cases of high risk of interventions, in particular, in voluminous nodular hyperplasia [2, 72].

Tiktinskii O. (2006) states that transurethral resection is welcomed in BPH with nodules up to 50 mm^3, maximum size – 70 mm^3 [73]. Later, Vasilchenko M. et al. (2012) mention that open transvesical prostatectomy remains will remain for a long time as one of the approaches of choice despite the advantages of unquestionably proposed medicinal and interventional mini-invasive treatment in recent years [74].

On this subject, many authors in recent years have focused on comparing between transurethral and open transvesical method. The latter being described as an intervention with major complications, such as: hemorrhage from the adenoma site from 250-2500 ml, intensive hematuria, inflammatory processes (urethritis, prostatitis, cystitis) including at the level of residual prostate, urinary infiltration, obstructive processes (urocystic cervical sclerosis, urethral stricture,), urinary incontinence, as well as high mortality ≥2.2% [75, 76]. At the same time, the authors mention that open method transvesical adenomectomy is accessible in different prostate adenoma volumes, including especially those complicated with diverticulum, concrements, tumors, etc., with excellent results characterized by minimal bleeding and in patients with heart failure and other comorbidities, but some disadvantages in the evolution of complications in the intra- and early and late postoperative period are also accentuated.

Among the most common complications are: hemorrhage and inflammation of the prostate adenoma site, such as urethritis, urethral fever, bacteriotoxic shock, thromboembolic syndrome, and at a distance the formation of bladder lesions, stenosis and structures of the urocyst cervix and prostate urethra, the prevention of which is a serious problem, being insufficiently solved so far [77, 78]. In this respect, we note that complications in open adenomectomies has a frequency from 12.5 to 30.9% based on multiple factors [79, 80].

All factors that can induce complications can be divided into two categories: general factors that are evaluated and corrected preoperatively and local factors, which are dependent on the urinary tract and some unforeseen complications that can occur during the enucleation process, non-effective intraoperative hemostasis, urine infiltration, parallels of the neuro-muscular component especially in the voluminous adenoma and others such as insufficient drainage of the surgical site, etc. Prevention of intraoperative and postoperative complications to date is determined by the features of hemostasis performed both locally, at the level of the surgical adenoma removal and regionally [81].

The lack of a unified vision on the causes and nature of complications after transvesical prostatectomy in order to improve hemostasis has been proposed several methods both transvesical and extravesical directed to stop bleeding as one of the major complications. Depending on the methods used for hemostasis, they are currently divided into mechanical-thermal, surgical and chemical. The extravesical ones included various mechanical-thermal actions (compression by transrectal balloon); suturing with vessel embolization, hypothermia, monitored hypotonia, which has become a thing of the past in BPH surgery. Ineffective mechanical-thermal methods include the use of electric current (electrocoagulation), which is unreasonable because causes deep necrolytic processes, the progression and persistence of cystitis, the formation of scars and strictures [78, 82].

To avoid bleeding from the surgical site, it is recommended to process it with hot 0.9% NaCl solution, or with ice (hypothermia), including with 3% H_2O_2 solution or 6%, buffering the box with gauze and by various changes of suturing the box with over 200 procedures. Relatively effective is also considered electrical stimulation of the surgical site using the transurethral electric catheter proposed by Shumakova E. (2000), which currently is being used for insignificant intra-operative hemorrhage [83, 84].

In contradictory discussions so far are also transvesical surgical methods such as draining the bladder using the Foley catheter, as well as methods of suturing the box and permanent or remove hemostatic connections [17]. Regarding the application of sutures, the data from the specialized literature prove that in the most common cases, they do not lead to an effective stop of complications during surgery or postoperative, which induce the emergence of favorable conditions for the development of acute or chronic inflammatory processes, including the sclerosis in the urocystic cervix and the prostate urethra [46, 72].

In the handling of intraoperative hemostasis at the surgical site after prostatectomy, the chemical method based on the use of hemostatic materials in the form of adhesives, collagen plasters containing fibrinous substances, which contribute to coagulation, is widely used, and the collagen substrate forms an impermeable barrier for air, detersive removal in regenerative processes. These are used as a method of choice [17].

To achieve a hemostatic effect with better visualization of the operating field, scientific research has been undertaken that is directed towards achieving perfect hemostasis. Recent studies conducted by Nazarov E. (2009) dedicated to the effectiveness of the use of absorbent hemostatic plasters at the level of the surgical site applied on the entire surface with the fixation of the hemostatic plaster through the Foley catheter balloon and using the closed irrigation system of the urocyst with antiseptics [83].

Another study carried out by Vitruk Iu. (2010) in the decompensated cases of the diverter consists of the application of temporary sutures on the cervix of the urocyst and the concomitant separate drainage of the urocyst and the surgical site after open adenomectomy [85]. The authors note that due to the methodologies used, the reduction of complications in the postoperative period as well as the reduction of obstructive processes and bed day was achieved. In this respect, the majority opinion with reference to the proposed methods for the improvement of the lodge hemostasis after adenomectomy and the reduction of inflammatory processes are estimated to be ineffective further. In this context, Komlev D.L (2004) noted that the particularities of management to improve hemostasis in the surgical site after the removal of benign nodular hyperplasia of the prostate is the "golden dream" of urologists and the effectiveness of innovative technologies used [69].

However, so far the majority of opinions referring to the priority of endoscopic versus classical transvesical interventions are diverse and sometimes contradictory, because, with the significant increase in the dynamism of the expenses of endoscopic interventions, they constitute an impressive medical-social and economic impact. Some sources mention that this impact is determined by the increase in the number of the population of advanced age relative to the working-age population [86].

Joseph E. (1992) mentions that in the US about 400,000 men manifest the symptoms of BPH. Speakman V. et al. (2004) also warned that referring patients to a doctor with diagnosis symptoms of BPH in recent years marks an incidence of 113-125 cases per 100,000 men. In the US direct expenditure on surgical assistance alone in BPH annually averages about $1.1-1.5 billion, and conservative treatment with alpha blocker inhibitors reached the limit of $800 million [3, 86-88], and this fact differs greatly from the economic possibilities of many European states, including Moldova.

At the same time, some authors mention that the increased level of morbidity and the high costs of transurethral interventions have favored the use of various alternative conservative treatments in BPH. Mini-invasive interventions are successfully applied in many economically developed countries, as a rule in small- and medium-volume BPHs, while for voluminous BPHs they are often unsuccessful, so transvesical open interventions have remained up-to-date to this day [89]. It is worth mentioning that the mortality rate in transvesical interventions is on average 3.3% in different countries with various public health systems, it is variable and dependent on the economic level - financial allocations and innovative technological resources available [29, 69, 75].

The data from the specialized literature in the last decades demonstrate the presence and persistence of advantages and disadvantages to the problem of BPH treatment, their basis is the diversity of surgical and conservative therapy approaches, the incidence of intra– and postoperative complications, especially the ineffectiveness of hemostasis methods after adenomectomy, the increasing incidence of patients with voluminous BPH (≥80 and 100 $cm^{3)}$, the economic-financial impact in medicine [77, 90]. Voluminous adenomas and mini-invasive technologies are also a significant burden for private medicine. According to Saigal C. (2005), the medical costs for treating BPH, direct and indirect, are estimated to be $3.9 billion annually. Thus, the findings in terms of cost-effectiveness meanings provide convincing evidence for clinicians, financiers, and policy makers to help differentiate minimally invasive surgical treatment and transverse open interventions in BPH [91].

Therefore, in conclusion, it is worth mentioning that the evolution of BPH is a complex and integrated process, with a heterogeneous etiology and involves a number of mediators and factors with mutual interactions, which with age induce an increase in the frequency of complications from the lower urinary tract (prostate, urethra, urocyst) and postoperatively with significant repercussions at a distance in the use of open transvesical adenomectomy or by mini-invasive methods as methods of selection; and especially in voluminous BPH. It remains questionable the infectious-inflammatory factor as the etiopathogenetic predictive moment of the prostate adenoma were secondary in the pathogenesis of intra- and postoperative complications in voluminous BPH which is imposed as a problem of great topicality with an obvious impact in the development of an effective therapeutic and medical-surgical treatment strategy at the level of the lodge. A problem for the first time is the study of inflammatory histomorphological peculiarities in prostate adenoma as well as at the limit of enucleation

and lodge after enucleation of the hyperplastic pathological process, which motivates the need to conduct a complex correlational histomorphological and immunohistochemical study in assessing the associations or coexistence of BPH and prostatitis.

An important aspect in the effective implementation of open transvesical interventions is the need to perform an effective hemostasis during surgery and the postoperative period that will allow monitoring of the activity of proteolytic processes at the level of the prostate adenoma and blood serum, PSA and alkaline phosphatase, the assembly of which will allow the definite optimization of therapeutic, medical-surgical treatment with significant reductions in postoperative complications. The lack of a real method that would diminish postoperative complications and raise the possibilities of monitoring and evaluating the general homeostasis and at the surgical site is a desideratum of research for the first time.

Conclusions

There remains the issue of reducing intra- and post-operative complications in BPH, especially the voluminous one, which imposes itself as a very topical problem in the development of an effective treatment strategy. For the first time a problem is the study of the particularities of some biochemical criteria at surgical site and in blood serum, histological - at the level of nodular prostatic hyperplasia and at the border of the prostate adenoma, which motivates the need for a complex correlational of biochemical, histological and immunohistochemical facts, including in the evaluation of the associations or coexistence of BPH and chronic prostatitis.

Competing interests

None declared.

Author's contribution

All the authors have contributed equally at the results presentation in the paper, approved the „ready for print" version of the manuscript.

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CASE STUDY

OPEN ACCESS

Prolonged sinus pauses after the paroxysms of atrial tachycardia in children, to pace or to ablate? Case report

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ABSTRACT

Background. The presence of prolonged sinus pauses is quite rare in children and adolescents with structural normal heart. The decision of the optimal therapeutic tactics is always challenging.

Case report. The 16-years-old girl addressed with complains of palpitations and dizziness after the palpitations end. A Holter ECG monitoring was performed with the detection of prolonged sinus pauses after the paroxysm of atrial tachycardia. We decided to perform an electrophysiological study to diagnose the tachycardia type. The presence of atrial tachycardia originating from the ostium of the coronary sinus was demonstrated. We decided to manage the tachyarrhythmia with catheter ablation. During the application of the radiofrequency currents, the tachycardia stopped, and the sinus rhythm was restored. The ablation was preferred over medication taking into consideration the potential risk of worsening of the bradycardia by antiarrhythmic therapy.

Conclusions. The optimal therapeutic solution in similar pediatric cases should be directed towards the supraventricular tachycardia treatment and not to the bradyarrhythmia. The majority of supraventricular tachycardias could be cured by catheter ablation.

Keywords: catheter ablation, children, pacemaker, sinus pause, supraventricular tachycardia.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Supraventricular tachycardia is frequently diagnosed in children. However, prolonged pauses after the tachycardia ends are still challenging for clinicians. There are insufficient data describing the management of the prolonged sinus pauses in children, including the pauses after supraventricular tachyarrhythmia.

The novelty added by manuscript to the already published scientific literature

We confirmed the relationship between sinus pauses and atrial tachycardia, and the possibility their definitive treatment by catheter ablation.

Introduction

According to the medical literature, the presence of prolonged sinus pauses is quite rare in children and adolescents with structural normal heart. It has been diagnosed with increasing frequency in children and young adult patients with congenital heart defect, especially in patients who have undergone corrective cardiac surgery related with atrial tissue [1]. In addition, abrupt termination of a supraventricular tachycardia (SVT) can be associated with sinus pauses due to overdrive suppression of the sinus node [2] (Fig. 1). In the described case we faced the choice of implanting a cardiac pacemaker or treating the supraventricular tachycardia by ablation.

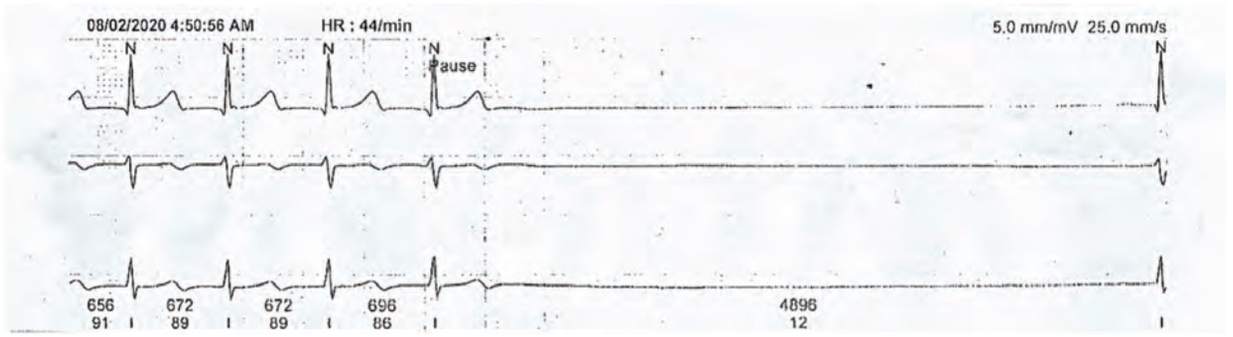

Fig. 1 Sinus pause.
An example of a sinus pause (4896 ms) after the termination of the supraventricular tachycardia recorded on Holter ECG monitoring

Case report

We present a case of 16-years-old girl who had atrioventricular nodal reentrant tachycardia (AVNRT) soon after birth. At 3-years-old, she had an ablation of AVNRT (2008), after which the patient remained asymptomatic for a long time. After 12 years the patient addressed with complaints to frequent episodes of rapid heartbeats followed by dizziness. We performed Holter ECG monitoring and found paroxysms of atrial tachycardia that ended with 970 sinus pauses > 2500 ms, the longest pause was 7376 ms (Fig. 2).

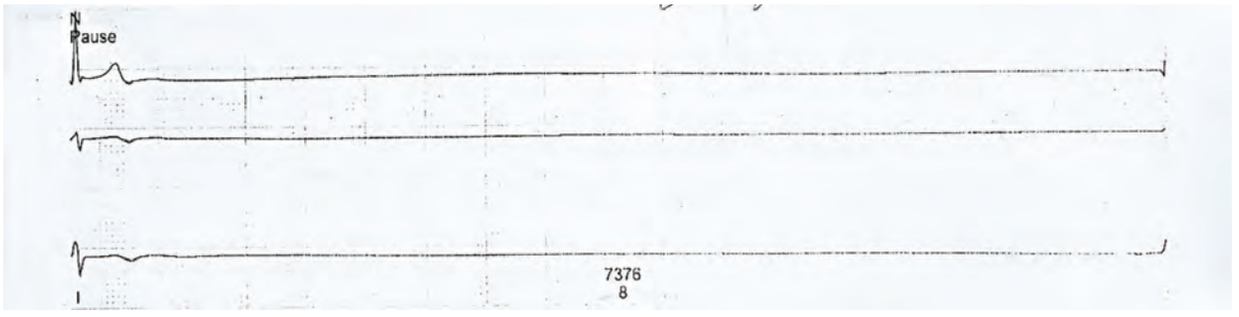

Fig. 2 The longest pause.
The pause of 7376 ms caused by sinus node asystole after an episode of supraventricular tachycardia,recorded in our patient on Holter ECG monitoring

We decided to avoid pacemaker implantation taking in consideration the young age and clear relationship between atrial tachycardia and sinus pauses. Our strategy was first to perform an electrophysiological study to diagnose the tachycardia type. Two diagnostic quadripolar catheters were placed into the high right atrium and the coronary sinus. A deflectable ablation catheter was used for mapping the atrial tachycardia.

The presence of atrial tachycardia originating from the ostium of the coronary sinus was demonstrated, during the application of the radiofrequency currents, the tachycardia stopped, and the sinus rhythm was restored.

The patient was evaluated by the Holter ECG after 1 month and 6 months, and neither atrial tachycardia, nor sinus pauses were found. She is remaining asymptomatic.

Discussion

Sinus node dysfunction with long sinus pauses is rare in children with structurally normal heart [1, 2]. There are a lot of data demonstrating that overdrive suppression of

the sinus node in the context of atrial fibrillation may result in sinus pause. This phenomenon is quite rare in children [3, 4]. Reports about adults have shown that ablation of the atrial fibrillation can lead to resolution of the sinus pauses. Some researchers reported the use of the same strategy in children [4].

After discussing with the parents and the patient all the possible management scenarios, we decided to manage the tachyarrhythmia with catheter ablation. The ablation was preferred over medication because of the potential risk of worsening of the bradycardia due to antiarrhythmic therapy. The decision was influenced by the fact that our patient supported ablation of AVNRT in the past, has a normal cardiac structure and function on echocardiography.

Pacemaker placement would have been a permanent intervention with possible future side effects such as infection, lead dislodgement, and cosmetic defect. Ablation was preferred as a definite procedure.

Conclusions

Even in some young patients, paroxysmal SVT could be complicated with long sinus pauses. The optimal therapeutic solution should be directed towards the SVT treatment and not to the bradyarrhythmia. The majority of SVT could be cured by catheter ablation.

Competing interests

None declared.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Authors' contributions

All the authors have contributed equally at the results presentation in the paper.

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CASE STUDY

OPEN ACCESS

Delayed successful interbody fusion after initially failed midline lumbar interbody fusion spinal arthrodesis in a patient with degenerative lumbar spondylolisthesis and severe osteoporosis

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ABSTRACT

Introduction. Dual x-ray absorptiometry (DEXA) scan has been the gold standard for assessing bone mineral density prior to spinal instrumentation surgery. DEXA scans, on the other hand, can produce falsely elevated measurements in patients with severe degenerative changes, compression fractures, and aortic calcification, which can lead to incorrect patient selection and failed interbody fusion.

Materials and methods. Detailed anamnesis of disease development, thorough clinical examination, patient-reported outcome measures (pain VAS, ODI, SF-12), preoperative and postoperative bone-window CT of the spine (interbody fusion status assessment), vertebral bone mineral density assessment by DEXA scan, vertebral bone density measurement in Hounsfield units by computer tomography, and the review of published literature were analysed.

Results. A 67-year-old woman was diagnosed with L4-L5 degenerative spondylolisthesis. DEXA scan revealed normal bone mineral density in the lumbar vertebrae. The patient underwent midline lumbar interbody fusion (MIDLIF). The postoperative course was complicated by the occurrence of clinical and radiographic signs of pseudarthrosis. She refused revision surgery and was lost to follow-up. Three years postoperatively, she presented in good physical condition, with significant improvement in pain and functional disability. A CT scan showed delayed successful interbody fusion with complete resolution of radiolucency around implants.

Conclusions. This case report summarizes some of the possible errors in diagnosis and surgical treatment in patients with degenerative pathology associated with severe vertebral osteoporosis.

Keywords: midline lumbar interbody fusion, MIDLIF, pseudarthrosis, DEXA, Hounsfield units.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

The reliability of cortical bone trajectory pedicle screw fixation of the spine in patients with severe osteoporosis has not been proven. The normal course of symptomatic pseudarthrosis after MIDLIF arthrodesis is unknown. The management of these patients has yet to be established.

The research hypothesis

A DEXA scanner may provide erroneous data on vertebral bone density in a specific group of patients with severe degenerative spine disease, which may cause patient selection bias and failure of spinal interbody fusion.

The novelty added by manuscript to the already published scientific literature

The study highlights possible causes of unrecognized vertebral osteoporosis in patients scheduled for spinal instrumentation surgery, which led to failed interbody fusion and symptomatic pseudarthrosis. A reliable way to diagnose vertebral osteoporosis using computed tomography was described, and the timing of surgical treatment of pseudarthrosis was established.

Introduction

The treatment of degenerative spinal instability in patients with severe osteoporosis remains controversial because of frequent instrument failure and the high rate of symptomatic pseudarthrosis. Pedicle screw loosening is correlated with an increase in back pain, leading to high disability and poor quality of life for patients. Cortical bone trajectory (CBT) screw fixation is considered a potential option for patients with osteoporosis undergoing lumbar fusion. The novel method of CBT screw fixation was introduced in 2009 by Santoni et al. [1]. The proposed trajectory offered the benefit of maximized thread contact with the zone of higher bone density in the pars interarticularis region, which is mostly spared by the osteoporotic disease process. The aims of this track were to improve the anchoring of the screws in osteoporotic vertebrae and to prevent instrumentation failure. However, the efficacy of CBT fixation in osteoporosis patients has not yet been proven.

Materials and methods

Detailed anamnesis of disease development and postoperative course, thorough clinical and neurological examination, patient self-reported outcome measures (pain VAS, ODI, SF-12), preoperative and postoperative bone-window CT of the spine with three-dimensional reconstructions for interbody fusion status assessment, vertebral bone mineral density assessment by DEXA (dual X-ray absorptiometry) scan, vertebral bone density measurement in Hounsfield units by computer tomography, and the review of published literature were analysed.

Results

We report the clinical case of a patient who underwent spinal stabilization surgery that failed due to poor vertebral bone quality, although preoperative tests showed adequate bone density. Considering the unusual postoperative course and the failure of the applied treatment, it was decided to analyse the patient's clinical and imaging data repeatedly with the application of new alternative bone density assessment methods. The literature reporting similar complications was also reviewed.

Clinical case

A 67-year-old woman was admitted to the neurosurgery ward of the *Timofei Mosneaga* Republican Clinical Hospital of Moldova with complaints of severe low back pain (VAS = 9/10) with irradiation in both lower limbs, predominantly in the left leg, without evident motor deficit. The patient has been suffering from low back pain for about 2 years. She has tried multiple treatment regimens, including complex physiotherapeutic and rehabilitation treatment, with only modest pain relief. The functional status was assessed using the Oswestry Disability Index, which corresponded to a state of crippled patient (ODI = 67%).

The patient underwent a lumbar spine MRI scan, which revealed the presence of a low-grade degenerative spondylolisthesis at the L4-L5 level, as well as bilateral foraminal stenosis, particularly narrow on the left side (Fig. 1).

Computed tomography demonstrated the presence of L4-L5 severe degeneration, with intradiscal vacuum phenomenon, facet joint deformity and hypertrophy, and left side foraminal narrowing due to a bony spur (Fig. 2).

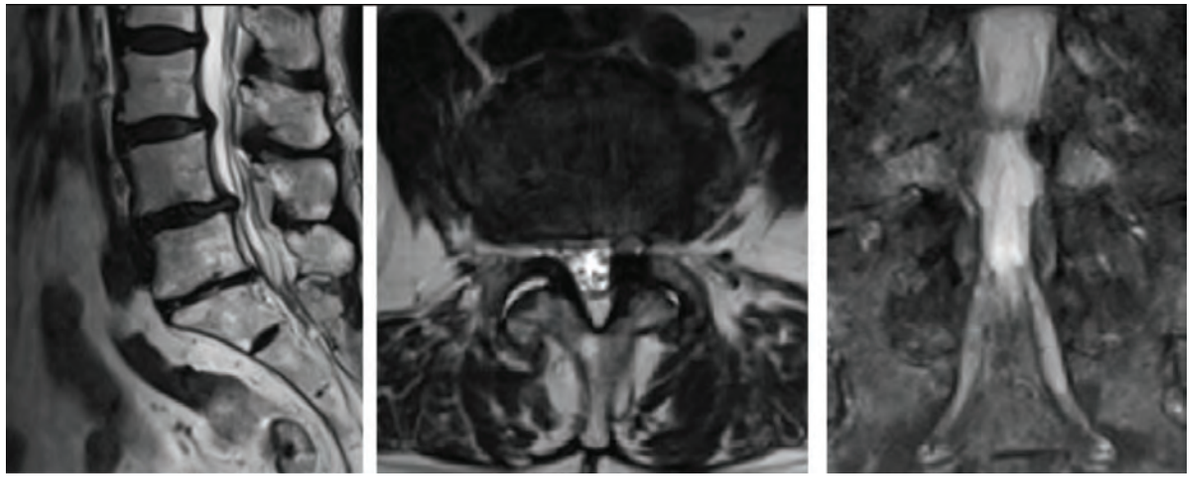

Fig. 1. MRI of the lumbar spine showing L4-L5 degenerative spondylolisthesis and foraminal narrowing.

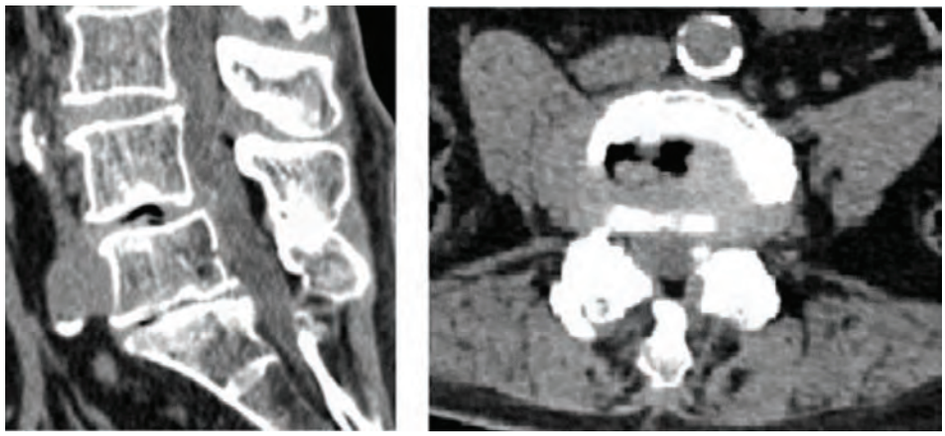

Fig. 2. CT of the lumbar spine showing severe L4-L5 and L5-S1 degeneration, with vacuum phenomenon and L4-L5 spondylolisthesis.

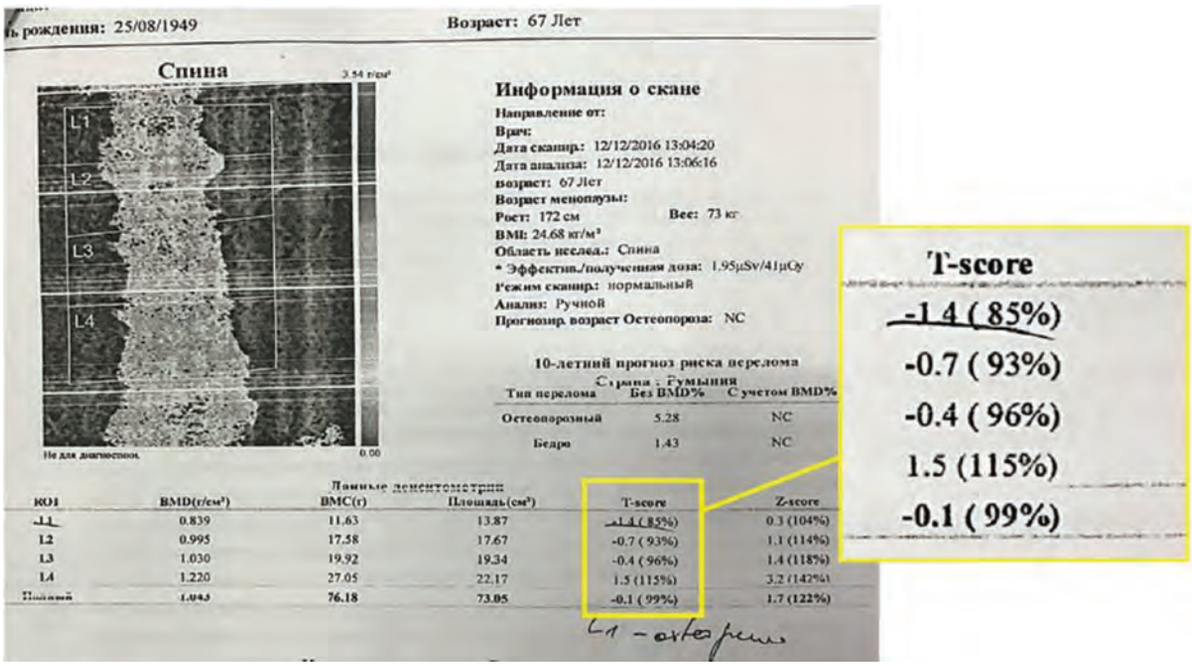

Fig. 3. DEXA scan showing normal bone density of the lumbar vertebrae, except L1.

The patient's vertebral bone density was assessed using dual x-ray absorptiometry (DEXA) scan, which demonstrated normal density of the lumbar vertebras. DEXA T-score was greater than -1 in all lumbar vertebrae except L1, which had a score of -1.4, corresponding to osteopenia (Fig. 3).

Treatment

Considering the association of symptomatic foraminal stenosis with degenerative spondylolisthesis and normal bone density of the lumbar vertebrae, indications for interbody arthrodesis were established. It was decided to apply the minimally invasive technique of midline lumbar interbody fusion (MIDLIF) with neuronavigation-guided CBT screws. This procedure involves the insertion of CBT pedicle screws and intervertebral cages through a limited medial exposure, similar to the laminectomy approach.

The procedure was done under general anaesthesia, with the patient being placed in the prone position. The level to be fused was identified using fluoroscopy. After a dose of antibiotics 30 minutes before the operation, a 5 cm posterior midline skin incision was made. The subperiosteal muscle dissection was limited to the lateral side of the pars interarticularis and facet joints. The neuronavigation-guided drill was used to create a pilot hole for the CBT screw at the junction of the superior articular process and pars interarticularis, following a medial-to-lateral path in the axial plane and a caudo-cephalad path in the sagittal plane. After the trajectory was created and tapped, CBT pedicle screws were placed bilaterally along the tracks (Fig. 4). A thorough posterior decompression, including bilateral facetectomy and total discectomy, was carried out. The endplate cartilage was removed, and the intervertebral cage was placed.

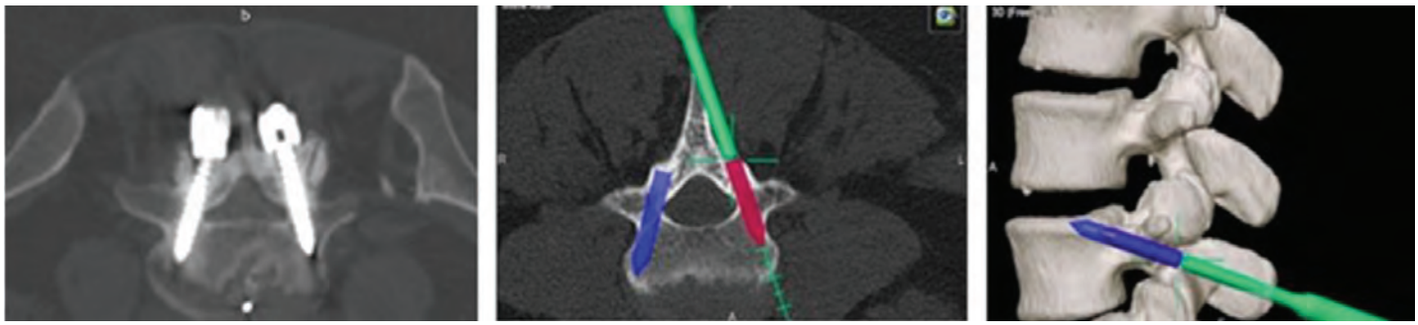

Fig. 4. Neuronavigation guidance of the CBT pedicle screws (right and centre) and the postoperative CT control of the screw position (left).

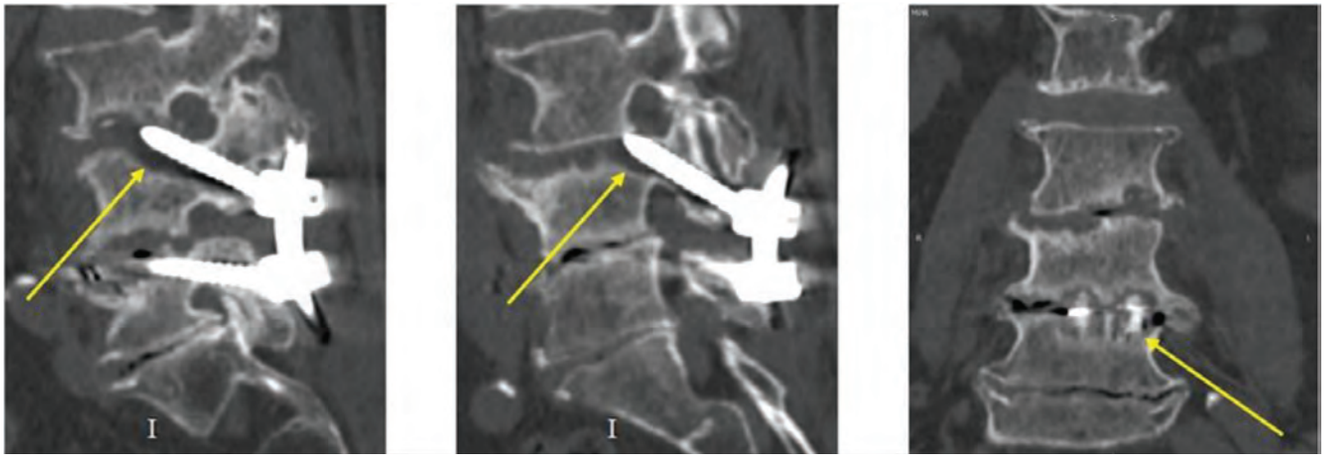

Fig. 5. 3 months after surgery, X-ray control reveals instrumentation failure with cage subsidence and dislocation of the upper CBT pedicle screws.

The cages and the disc space were filled with autogenous bone obtained from the decompression to provide interbody fusion. The self-retaining retractor was removed, and the wound was closed in a standard way. A sterile wound dressing was applied.

Outcome and follow-up

The patient was allowed to walk the first day after surgery. Significant postoperative relief of radiating pain in the lower limbs was obtained. Moderate pain (VAS = 3-4 p.) and discomfort remained in the postoperative wound area, which was well controlled by non-steroidal analgesics. The patient was discharged from the hospital two weeks after surgery. She was encouraged to avoid sitting for long periods and heavy lifting during the first 3 months after surgery.

At 3 months postoperatively, the patient presented with severe pain (VAS = 8p.) in the lumbar region, without radiation to the lower limbs. A follow-up radiograph was performed, which showed signs of mechanical failure of the screw fixation system, with dislocation of the proximal pedicle screws in the cranial direction and subsidence of the interbody cages (Fig. 5).

The patient was advised to wear a lumbar brace and take special medication (vitamin D and calcium) to accelerate the process of interbody fusion. The CT scan control was scheduled for 6 months after surgery.

At the 6-month follow-up point, the patient presented with persistent axial low-back pain (VAS = 6p.), radiating in the lower limbs (VAS = 4p.). The ODI score was 42%, corresponding to a severely disabled patient. A computer tomography scan showed clear signs of radiographic pseudarthrosis, with loosening and migration of the cranial screws, subsidence of interbody cages, and a significant radiolucent halo around implants (Fig. 6).

The patient was offered the option of revision surgery with removal of the CBT screws and fixation of the spine with traditional pedicle screws augmented with vertebroplasty cement. The patient decided to decline the proposed treatment for her own reasons. She was allowed to continue conservative treatment under the supervision of her family doctor.

She was unable to follow up after that. Being a participant in a scientific trial, she was called for a final examination at the 3-year follow-up point. She presented only with mild low back pain (VAS = 2p.) without radiating pain. Her ODI score improved to 18%, which correlated with a state of only mild disability. A lumbar spine CT scan confirmed the presence of solid interbody fusion (BSF-3) and the absence of radiolucency around the implants (Fig. 7).

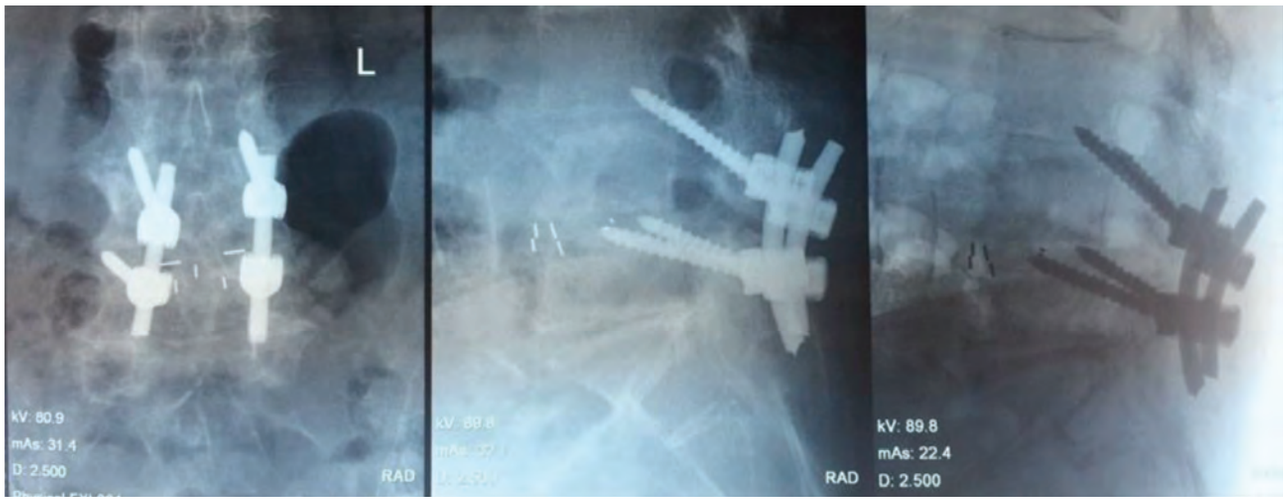

Fig. 6. CT scan at the 6-month follow-up point, showing signs of radiographic pseudarthrosis with radiolucency around screws and cages, screw dislocation, and cage subsidence.

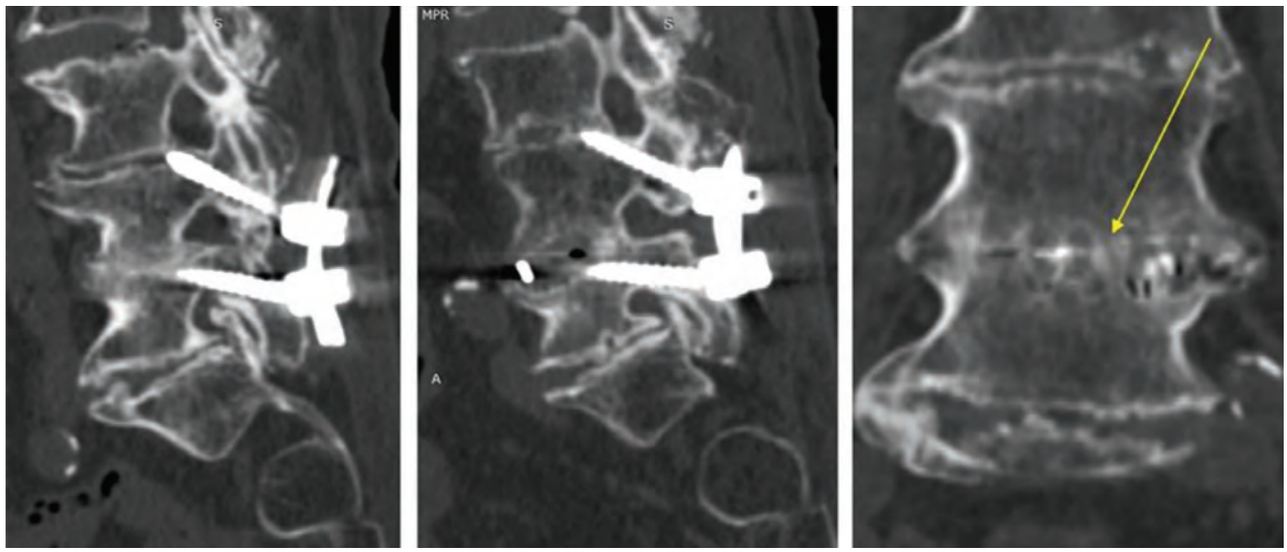

Fig. 7. Three-year CT scan demonstrating delayed successful L4-L5 fusion, with continuous bony fusion mass inside and outside the cages (arrow), and resolution of radiolucency around the implants.

Discussion

Insufficient grip strength leading to mechanical hardware failure is a well-known drawback of traditional pedicle screws, especially in osteoporotic patients. CBT pedicle screws have been proposed as a solution to reduce the rate of screw loosening due to the purchase of higher-density bone in the pars interarticularis area.

The DEXA scan has been the gold standard for assessing bone mineral density (BMD) prior to spinal instrumentation surgery. However, DEXA scans can result in falsely elevated BMD measurements in patients with severe degenerative changes, compression fractures, and calcification of the aorta.

In our case, the DEXA scan showed a normal BMD of the lumbar vertebrae. To explain the failure of arthrodesis, preoperative computed tomography data were reviewed, and the method of bone quality assessment described by Zaidi et al. was applied [2]. This method involves measuring the density of cancellous bone tissue at the level of the L1 lumbar vertebra, with a threshold value of 110 HU being highly (> 90%) specific for osteoporosis. A free trial version of RadiAnt DICOM Viewer software was used to measure vertebral bone density. A density of 57 HU was found in the cancellous bone of the L1 vertebra (Fig. 8), which correlates with the presence of severe osteoporosis and explains the pseudarthrosis formation.

Our observations corroborate with those of other studies [3-5] that state that a DEXA scan alone is insufficient for an accurate diagnosis of vertebral osteoporosis when important degenerative changes or vascular calcifications

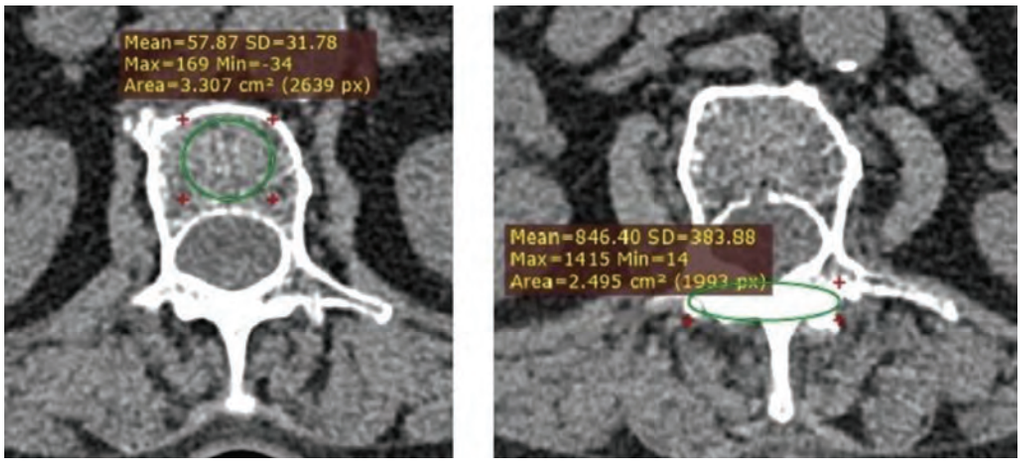

Fig. 8. CT scan assessment of cancellous bone density (left) and cortical bone in the pars interarticularis region (right) of the L1 vertebra.

are found in preoperative lumbar radiological examinations.

Pseudarthrosis remains one of the most challenging problems facing the spinal surgeon. It is usually defined as failure of bony union between two vertebrae within one year after surgery, indicated by the absence of continuous trabecular osseous bridging between vertebrae, peri-implant radiolucency on CT, and motion on flexion-extension radiographs. The patient with symptomatic pseudarthrosis usually presents with worsening axial back pain. After the diagnosis of pseudarthrosis, depending on the clinical situation, there are many different treatment options. The primary principles include stabilization of the existing posterior fixation by replacing the loose pedicle screws, followed by additional bone grafting.

However, there is no unanimous consensus on when a patient with pseudarthrosis should undergo revision surgery. Tokuhashi et al. declared that it is not reasonable to define a failure to achieve osseous union within one year after posterior spinal surgery as pseudarthrosis and that the condition should instead be called delayed union [6]. They reported that the postoperative pedicle screw radiolucent zone disappeared over time in approximately two-thirds of patients treated with posterior lumbar arthrodesis, and its presence did not necessarily indicate permanent pseudarthrosis [7]. Another study published by Kanemura et al. (2014) stated that the interbody arthrodesis site in patients with early pseudarthrosis may begin to change to a successful fusion one or two years after surgery, with two-thirds of such patients exhibiting successful fusion five years after surgery. They concluded that a final determination of nonunion or delayed union after posterior lumbar interbody arthrodesis should be made three years after surgery [8].

Conclusions

- A DEXA scan can result in falsely elevated BMD values in patients with spinal degeneration, severe spine deformities, or vascular calcifications. A CT scan could be successfully used to assess bone quality before instrumented spine surgery.
- The measurement of bone density in Hounsfield units is rapid, simple, and reproducible. A cut-off value of 110 HU measured in the L1 vertebra is considered highly specific for osteoporosis. These patients are at risk for screw loosening, subsidence, and pseudarthrosis. Careful surgical treatment planning is essential for this type of patient.
- Even if the majority of trials suggest that CBT-screw fixation is a reasonable and superior alternative to traditional pedicle screws for osteoporotic populations, the risk of hardware failure in these patients remains very high, imposing the need to consider safer alternatives such as cement-augmented pedicle screws.

A final assessment of the pseudarthrosis should be performed at least three years after surgery.

Abbreviations

BMD – bone mineral density, CBT – cortical bone trajectory, CT – computer tomography, DEXA – dual X-ray absorptiometry, MIDLIF – Midline Lumbar Interbody Fusion, MRI – Magnetic Resonance Imaging, HU – Hounsfield unit.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

None declared.

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CASE STUDY

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Idiopathic hypertrophic osteoarthropathy misdiagnosed as juvenile idiopathic arthritis. Case study.

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ABSTRACT

Background. Pachydermoperiostosis (or primary hypertrophic osteoarthropathy) is a rare genetic disease that usually begins in childhood or adolescence, is characterized by certain clinical signs (pachydermia, periostosis, drum sticks) that gradually progress over many years until the disease stabilizes. Currently, there are 2 genes in which mutations are associated with the development of pachydermoperiostosis - HPGD and SLCO2A1. The functions of these genes are not fully understood, but their influence on the metabolism of prostaglandin E2 is known.

Case presentation. We present a case of a 20-year-old patient mistakenly diagnosed as juvenile idiopathic arthritis. Symptoms on admission to the hospital: pain accompanied by swelling in the hands and feet, arthralgias in the talocrural joints, knees with slight swelling, paresthesia in the extremities, hyperhidrosis, fatigue. Clinical and paraclinical examinations confirmed the diagnosis of pachydermoperiostosis.

Conclusions. Pachydermoperiostosis should be considered as a differential diagnosis when a patient presents with hypertrophic osteoarthropathy and acromegalic features.

Keywords: pachydermoperiostosis, primary hypertrophic osteoarthropathy, juvenile idiopathic arthritis.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Pachydermoperiostosis is a rare genetic disorder characterized by skin thickening, digital clubbing and periostitis. Clinical manifestations are not recognized timely, they often mimic rheumatic inflammatory diseases.

The research hypothesis

A comprehensive clinical examination supplemented by genetic testing and imaging is helpful in diagnosis.

The novelty added by manuscript to the already published scientific literature

We present a case of a rare disease mistakenly diagnosed as juvenile idiopathic arthritis. Thorough examination with analysis of anamnestic, clinical, imaging and genetic data are decisive in the correct diagnosis of PDP.

Introduction

Primary hypertrophic osteoarthropathy or pachydermoperiostosis (PDP) is a rare genetic disease with both autosomal dominant and autosomal recessive transmission. It is mainly found in males, who have more pronounced clinical manifestations; the male/female ratio is 9:1 [1]. This pathology affects the skin and bones and is characterized by the association of cutaneous manifestations (pachydermia or thickening of the skin) with rheumatological manifestations (periostosis and digital clubbing). Onset of the disease usually occurs at puberty, with thickening and wrinkling of the face (pachydermia), causing thickening of the facial features, ptosis of the eyelids and *cutis verticis gyrata* on the scalp. Another characteristic feature is the enlargement of the fingertips (digital clubbing), which can appear from childhood or in adolescence, sometimes remaining the only clinical manifestation. Structural changes can also occur in the osteo-articular system, manifesting by the swelling of the periarticular tissues and the bone proliferation of the tubular bones at the level of the periosteum (periostosis). The lower part of the legs can take on a cylindrical shape known as "elephant foot" [2]. Joint involvement can be characterized by arthritis, hydrarthrosis arthralgias, and hemarthrosis. Other clinical manifestations include seborrhea, acne, hyperhidrosis of the palms and soles, eczema, feeling of warmth in the hands and feet. PDP can be complicated with neurological manifestations and can be associated with structural cardiac manifestations. These changes usually progress 5-20 years, and then remain permanently stable. From a clinical point of view, PDP is divided into 3 subclasses: I – the complete form, which presents the phenotype in general, II - an incomplete form, with isolated bone involvement and limited skin changes, and III - a truncated form, with minimal or absent pachydermia and periostosis [3].

Case presentation:

A 20-year-old man was admitted to rheumatology department presents with the following complaints: pain accompanied by swelling in the hands and feet, pain in his both ankles, and knees with The onset of the disease was insidious, at the age of 14, when pain in the joints of both knees and ankles and low fever appeared, after several episodes of streptococcal pharyngitis. He received anti-inflammatory treatment in the rheumatology department of the pediatric hospital, being diagnosed with juvenile idiopathic arthritis. Treatment with NSAIDs and antibacterial medicines reduced pain intensity and joint swelling. Few months later, he noticed the appearance of pustular acne on his face and upper body. At the age of 15, he noticed a sudden increase in his height (+20cm) and in the size of hands and feet (from size 40 to 45), with swelling of soft tissues. He periodically had cold symptoms accompanied by arthralgia, during which he administered various types of NSAIDs. Considering the frequent colds, in 2018 he underwent a tonsillectomy, followed by the administration of benzathine penicillin for a duration of 6 months. In 2019, a pituitary tumor was ruled out after a brain MRI examination. In addition, thyroid scintigraphy in 2019 did not confirm any thyroid disease to explain the clinical symptoms.

During the physical examination, we noticed the presence of Hippocratic fingers on the hands and feet; diffuse swelling of the palmar and plantar soft tissues accompanied by hyperhidrosis (fig.1). At the level of the face, palpebral ptosis and thickening of the tegument are determined (fig 2A). At calf level - cylindrical deformity known as „*elephant extremities*" (fig. 2B).

Laboratory investigations show normal values of hematological parameters, as well as ESR, C-reactive protein, electrolytes, transaminases, bilirubin, total protein, albumin, coagulogram, uric acid, LDH, CPK, lipid profile, normal levels of thyroid indices (TSH, FT4). ECG, chest X-ray without pathological changes.

Genetic testing with next-generation sequencing (with lllumina NextSeq and Illumina Trusight One Expanded set) identified heterozygous variants NM_005630.3:c. 1658delT p.(lie553Thrfs*7) of the SLCO2A1 gene (Laboratorio di Genetica, Azienda Ospedale – Universita di Padova). Inactive variants of the SLCO2A1 gene are associated with autosomal recessive primary hypertrophic osteoarthropathy syndrome (MIM#614441).

Radiographic examination of hands, feet, and long bones of lower legs show cortical thickening of the metacarpals and proximal phalanges of both hands (fig. 3), significant

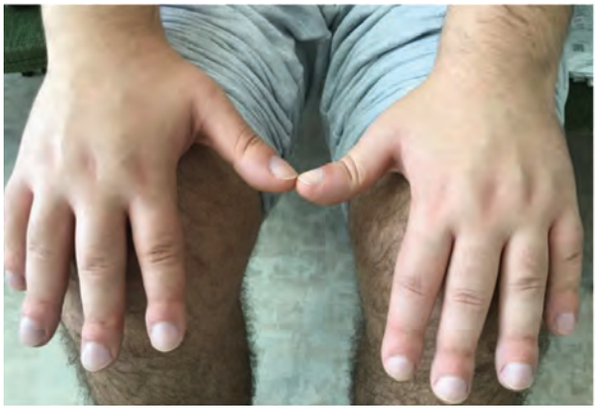
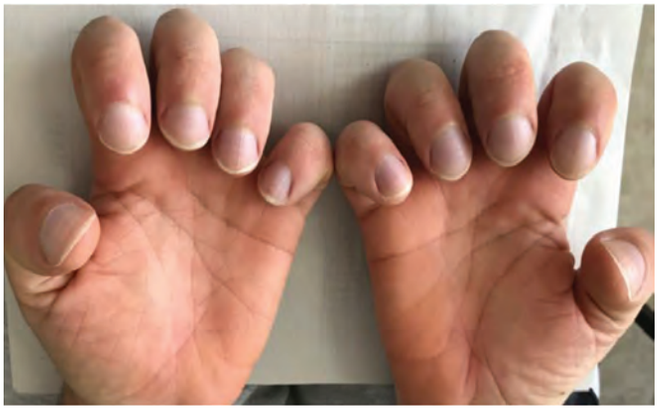
A   B

Fig. 1. Digital clubbing of the fingers
A. Hippocratic digits; B. Swelling of palmar soft tissues with hyperhidrosis.

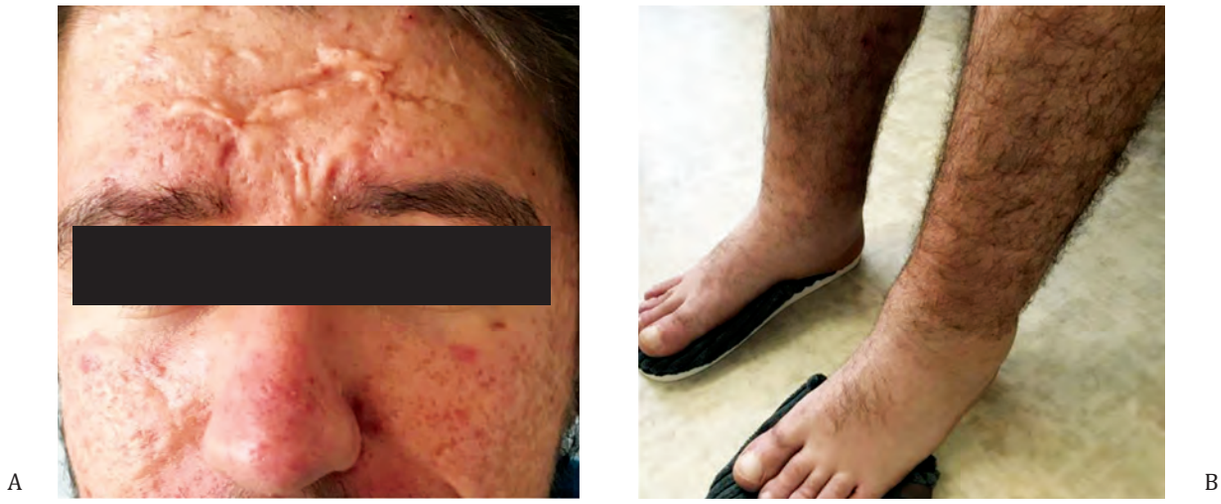


Fig. 2. Cutaneous thickening.
A. Palpebral ptosis and face skin thickening and wrinkled; B. „Elephant extremities"

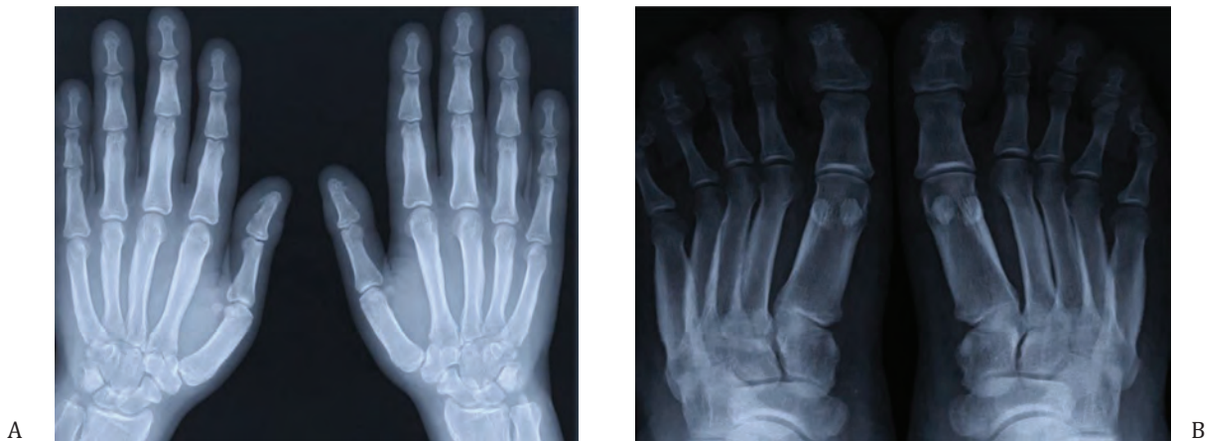


Fig. 3. X-ray examination of hands and feet.
A.Cortical thickening of carpal and metacarpal bones; B. Cortical thickening of tarsal and metatarsal bones

and irregular thickening of the periosteum - cortex of the femoral bones (fig. 4).

Based on the clinical and paraclinical results, we established the diagnosis: Primary hypertrophic osteoarthropathy (or Pachydermoperiostosis). Treatment with NSAIDs during the periods of arthralgias and joint swelling temporarily relieved the symptoms.

Discussions

Hypertrophic osteoarthropathy (HOA) is a clinical syndrome, manifested by the increase in size of the extremities as a result of bone and periarticular proliferation, Hippocratic fingers and toes, and painful swellings in the joints. This can be primary (PDP) and secondary. Secondary or pulmonary HOA is associated with a lung pathology, often lung cancer. It is important to make a differential diagnosis between these two pathologies, in order to determine the subsequent treatment process [1].

Referring to the presented clinical case, the age of onset of this pathology is specific – in adolescence. The patient presents the full form of the disease, with both dermatological and rheumatological clinical manifestations. The consecutiveness of the appearance of clinical manifestations is observed, starting with the increase in the size of the extremities, Hippocratic fingers, arthralgias, and osalgias and contin-

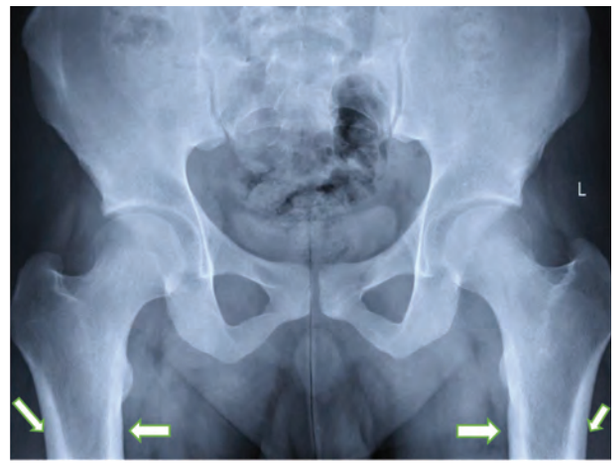


Fig. 4. X-ray examination of long bones in the lower legs (femoral bones).
Irregular profiles of the proximal epiphyses of both thigh-bones

uing with the skin manifestations, which developed during puberty, thus making it difficult to establish the diagnosis. It is important that for about 1.5 years the patient has shown stagnation in growth, already suspecting a slowing down of the disease, which is known to occur after 5-20 years after the initiation of structural changes. According to the investigations carried out, no structural manifestations or increases in the size of the internal organs were determined. In addition, the laboratory analyzes and the hormonal profile are within the limits of the norms, which helps to establish the diagnosis of PDP. Due to such a varied clinical picture, it was initially difficult to determine the diagnosis and differential diagnosis was performed with several pathologies. Among them were acromegaly, secondary HOA, SAPHO disease.

To differentiate PDP from secondary HOA, it is necessary to examine the chest to rule out a lung mass. In the reported case, the presence of a formation in the lungs was not determined.

Authors had to differentiate it from the SAPHO disease. It is known that the manifestations in SAPHO appear late, mainly between 30-50 years, in the case of the patient it is known that it started in adolescence. Cutaneous manifestations differ in the presence of acneiform and pustular eruptions but thickening of the skin with changes in facial features, palpebral ptosis, and *cutis verticis gyrata* are not attested. In addition, the musculoskeletal manifestations in SAPHO disease have a more central spread, affecting the chondro-sternal, sacroiliac, coxofemural and knee joints. Nevertheless, peripheral joint damage and Hippocratic fingers are specific for PDP, these manifestations are present in the studied patient from this clinical case.

Acromegaly has similarities with PDP. The presence of Hippocratic toes and periostosis, plus the absence of prognathism, enlargement of the sella turcica, or abnormal circulating concentrations of growth hormone products would be helpful in establishing this diagnosis. According to the results of the laboratory data, the presented patient does not show any changes specific to this pathology.

Thyroid acropachy is characterized by periosteal proliferation located mainly in the small tubular bones of the hands and feet, being a rare manifestation of Graves' disease and independent of the state of thyroid function. Clubbing usually coexists with exophthalmos and pretibial myxedema. Myxedema resembles the elephant's feet described in HOA. The presence of digital clubbing for several years in the absence of a recognized internal disease is in favor the diagnosis of PDP.

It is necessary to differentiate this pathology from others, such as cranio-osteoarthropathy, chronic recurrent multifocal osteomyelitis, Camurati-Engelman disease, and syphilitic periostosis, in order to determine the correct treatment tactics. PDP is a self-limiting pathology with no effect on life expectancy. Symptoms stabilize or even resolve in the third or fourth decade, with an average interval of 10 years after the onset of symptoms. In the case of persistent joint and bone pain syndrome, the administration of analgesic medications and COX2-inhibiting NSAIDs have been shown to be effective in reducing arthritis. A regression of inflammatory markers (ESR, CRP) was determined when Etoricoxib was administered [4]. Rheumatologic symptoms may also be improved by treatment with bisphosphonates such as pamidronic acid or risedronate. Bisphosphonates inhibit osteoclastic resorption and therefore reduce bone remodeling and improve polyarthritis [4]. In the hospital, anti-inflammatory medication was administered, and at discharge, the arthralgia and swelling of the soft tissues decreased. The patient needs to be reevaluated periodically (every 3-6 months) after being discharged with recommendations of using COX2 inhibitors.

Conclusions

The diagnosis of pachydermoperiostosis is based on the clinical manifestations presented by the patient and requires more detailed laboratory evaluation to differentiate it from other similar pathologies. To confirm the diagnosis, it is necessary to find the presence of cutaneous (thickening and wrinkling of the face (pachydermia), thickening of facial features and ptosis of the eyelids and scalp producing *cutis verticis gyrata*) and rheumatological manifestations (Hippocratic fingers, swelling of periarticular tissues and bone proliferation of tubular bones at the level of periosteum (periostosis) manifesting as „elephant's foot"). It is imperative to know the diagnostic criteria in order to administer a specific treatment for this pathology. For PDP, symptomatic treatment with analgesics and COX2-inhibiting NSAIDs are indicated. In addition, some studies mention the importance of bisphosphonates in reducing the progression of hyperostosis.

Authors' contribution

All listed authors have provided a significant contribution to the collecting of material and writing this article. All authors revised and approved the final version of the manuscript.

Informed consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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All electronic references should include active and available URLs and the access date.

Examples of references

Journal article

Belîi A, Cobâleţchi S, Casian V, Belîi N, Severin G, Chesov I, Bubulici E. Les aspects pharmacoéconomiques dans la gestion de la douleur périopératoire [Pharmaco-economic aspects of perioperative pain management]. Ann Fr Anesth Reanim. 2012;31(1):60-6. French. doi: 10.1016/j.annfar.2011.09.008.

Book

Razin MP, Minaev SV, Turabov IA. Detskaia khirurgiia [Pediatric surgery]. 2nd ed. Moscow: Geotar-Media; 2020. 696 p. Russian.

Chapter in a book

Steiber AL, Chazot C, Kopple JD. Vitamin and trace element needs in chronic kidney disease. In: Burrowes J, Kovesdy C, Byham-Gray L, editors. Nutrition in kidney disease. 3rd ed. Cham: Humana Press; 2020. p. 607-623.

Conference paper

Ojovan V. Medical rehabilitation of children with type 1 diabetes: medical bioethical and psychosocial aspects. In: MedEspera: 9th International Medical Congress for Students and Young Doctors, 12-14 May 2022, Chisinau, Republic of Moldova: Abstract book. Chișinău; 2022. p. 77.

Website reference

World Health Organization (WHO). Therapeutics for Ebola virus disease [Internet]. Geneva: WHO; 2022 [cited 2022 Sep 5]. Available from: https://www.who.int/publications/i/item/9789240055742

TABLES AND FIGURES

Tables should be numbered consecutively with Arabic numerals, and be cited in text. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Tables must be submited as editable text and not as images. Each table should be completely informative in itself, and the data presented in it do not duplicate the results described elsewhere in the article.

The label "Table 1" and a short descriptive title should be provided above the table. Legends, notes, and any abbreviations used in the table should be explained below the table in a footnote. Applied statistical tests and the type of presented data should be also mentioned. Please follow the example:

Table 1. Intra-anesthetic and immediately post-extubation adverse events

	Experimental Cohort (n=100)	Control Cohort (n=100)	p
Dysrhythmia	6.0%	30%	0.49
Hemodynamic instability	7.0%	1.0%	0.034
Prolonged awakening*	11.0%	4.0%	0.19
PONV post-intubation	8.0%	27.0%	0.007
Strong pain on awakening	17.0%	19.0%	1.0

Note: *Unusually slow awaking, after that cerebral concentration of the anesthetic reach the under hypnotic level.
Used statistical analysis: Fisher's exact test.

Figures (photographs or radiographs, drawings, graphs, bar charts, flow charts, and pathways) should be submitted in a suitable format for print publication. Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. Figures' quality should assure the visibility of details. The following file formats are accepted: ".jpeg", ".tiff", ".eps" (preferred format for diagrams), ".ppt", ".pptx" (figures should be of the size of a single slide), with a resolution of at least 300 dpi.
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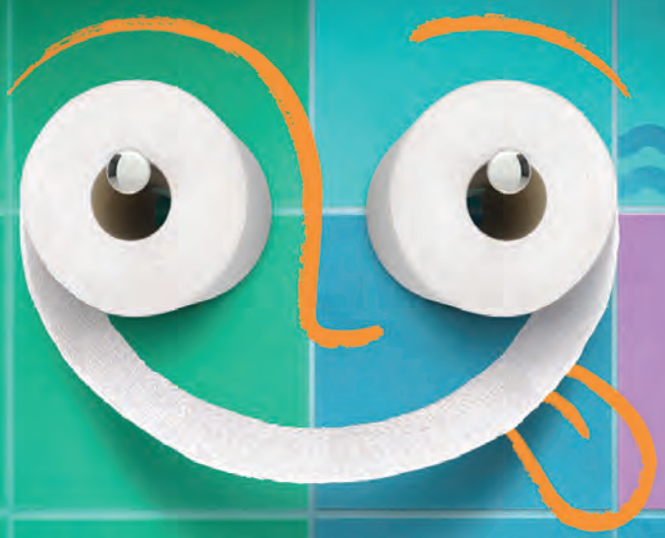

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POTRIVIT PENTRU TRATAMENTUL DURERII ACUTE[1]

Rezumatul caracteristicilor produsului medicamentos Brufen. Certificat de inregistrare în Republica Moldova de la 09.10.2019 nr. 25825, valabil pînă la 09.10.2024, cu modificări de la 07.04.2021. Forma farmaceutică - granule efervescente. Compoziție -1 plic conține substanță activă - ibuprofen 600 mg. Indicații terapeutice - ibuprofen este indicat în tratarea artritei reumatoide, inclusiv artritei reumatoide juvenile sau bolii Still, spondilitei anchilozante, osteoartritei și altor artropatii nereumatoide (seronegative) și artritei gutoase acute. De asemenea se utilizează pentru tratamentul afecțiunilor reumatice nearticulare și a afecțiunilor periarticulare, precum sindromul umărului înghețat (capsulita), bursita, tendinita, tendosinovita și a durerilor lombare. Ibuprofen este indicat în traumele țesuturilor moi, precum luxațiile și entorsele, pentru atenuarea durerilor ușoare și moderate, precum dismenoreea primară, durerile dentare sau postoperatorii, durerea după episiotomie, durerea după naștere și pentru atenuarea simptomatică a durerilor de cap, inclusiv a migrenelor. De asemenea ibuprofen este indicat pentru tratamentul febrei. Mod de administrare -administrare orală. Pentru a realiza un debut mai rapid al acțiunii, doza poate fi administrată pe stomacul gol. La pacienții cu afecțiuni ale tractului gastrointestinal medicamentul se administrează în timpul mesei. Înaintea administrării granulele trebuie dizolvate într-o cantitate mare de apă. La administrarea medicamentului poate apărea o senzație tranzitorie de arsură la nivelul cavității bucale sau gâtului. Adulții și adolescenții cu vârsta peste 12 ani (≥ 40 kg) Doza zilnică recomandată este de 1200-1800 mg, divizată în câteva prize. Pentru unii pacienți poate fi suficient 600-1200 mg pe zi. În cazuri severe și acute poate fi util de crescut doza până la finisarea fazei acute. Doza zilnică maximă nu trebuie să depășească 2400 mg, care se utilizează în câteva prize. Copii. Brufen în această formă farmaceutică este contraindicat copiilor cu vârsta sub 12 ani. Reacții adverse Profilul reacțiilor adverse la utilizarea ibuprofenului este similar altor AINS. Contraindicații. Reacțiile adverse la utilizarea de Ibuprofen nu se diferă de alte AINS. Efecte adverse frecvente. •Hipersensibilitate la substanța activă . • ibuprofenul este contraindicat pacienților cu astm bronșic, urticarie ori reacții de tip alergic în urma administrării de acid acetilsalicilic/aspirină sau alte AINS; • insuficiență cardiacă severă (NYHA IV); • insuficiență hepatică severă; • insuficiență renală severă (rata filtrării glomerulare sub 30 ml/min); • afecțiuni care implică o tendință crescută de sângerare sau sângerare activă; • antecedente de sângerări gastrointestinale ori perforații, în urma terapiei cu AINS; • colită ulcerativă, boala Crohn, ulcer peptic recidivant sau hemoragie gastrointestinală (două sau mai multe episoade distincte de ulcer sau hemoragii diagnosticate) prezente sau în antecedente; • trimestru trei de sarcină. Se eliberează la indicația medicului. Informația este destinată specialiștilor. Informația complete despre produs este indicată în prospectul pacientului și rezumatul caracteristicilor produsului medicamentos Brufen în Republica Moldova de la 07.04.2021 nr.25825. Producător- ABBOTT S.P.A. SS 148 (PONTINA KM 52.8) CAMPOVERDE DI APRILIA,04011 Campoverde di Aprilia,Italia.În prealabil eliberării și consumului, este necesară studierea aprofundată a prospectului pacientului și rezumatului caracteristicilor produsului medicamentos.

Rezumatul caracteristicilor produsului medicamentos Brufen Rapid. Certificat de inregistrare în Republica Moldova de la 11.08.2020 nr.26419 și nr.25420, valabil pînă la 11.08.2025, cu modificări de la 07.04.2021. Forma farmaceutică - capsule moi. Compoziție - 1 capsulă conține ibuprofen 200 sau 400 mg. Indicații terapeutice - tratamentul simptomatic pe termen scurt al durerilor ușoare până la moderate, cum sunt cefalee, dureri menstruale, dureri de dinți, durerii asociate simptomelor de gripă și febră la adulți și adolescenți cu greutatea de cel puțin 20 kg (de la vârsta de 6 ani în cazul utilizării Brufen 200 mg) și cel puțin 40 kg (de la vârsta de 12 ani în cazul utilizării Brufen 400 mg). Doze și mod de administrare. Pentru administrare orală și pe termen scurt. Capsulele nu trebuie mestecate. Adulți și adolescenți ≥ 40 kg (de la 12 ani și peste): doza inițială este de 1 capsulă (400 mg, administrată cu apă). Dacă este necesar, următoarea capsula poate fi administrată peste 6 ore. Doza pentru capsule 200 mg - copii cu greutatea de pînă la 39 kg. Preparatul Brufen Rapid poate fi utilizat pentru tratamentul copiilor cu greutatea de cel puțin 20 kg. Doza maximă de ibuprofen este de 20-30 mg/kg masă corporală, repartizată în 3-4 etape, cu intervalul de 6 – 8 ore. Nu este permis de depășit doza zilnică recomandată -pentru copii și maturi cu greutate de peste 40 kg-1200 mg în decurs de 24 ore, pentru copii cu masa corporală sub 39 kg- 30 mg/kg în decursul a 24 ore. Reacțiile adverse - cel mai des sunt întîlnite reacții adverse de ordin gastrointestinal. Este risc posibil de meningită aseptică, porfiria intermitentă acută, la persoanele vârstnice crește riscul dezvoltării consecințelor serioase ale reacțiilor adverse, în special hemoragie și perforare gastrointestinală, care pot fi letale, grețuri, vomă, diaree, constipație, balonare, tulburări gastrointestinale, dureri stomacale, tulburări de scaun, vomă cu sînge, colită ulcerative, ulcerația, boală Crohn, agravare simptomelor gastrointestinale, reacții de hipersensibilitate, reacții alergice nespecifice și anafilaxie, tulburări respiratorii obstructive cronice, deoarece pentru aceștia există un risc crescut de dezvoltare a reacțiilor alergice. Aceste reacții se pot manifesta ca un episod de astm bronșic, edem Quincke sau urticaria, reacții cutanate grave, unele dintre ele letale, incluzând dermatita exfoliativă și dermatoză buloasă.

Contraindicații - Hipersensibilitate la substanța activă, antecedente de reacții de hipersensibilitate sub formă de bronhospasm, astm bronșic, rinită, angioedem sau urticarie, asociate cu administrarea acidului acetilsalicilic sau a altor medicamente antireumatoide/ antiinflamatoare nesteroidiene (AINS),antecedente de hemoragii gastrointestinale sau perforație, determinate de terapia anterioară cu AINS,ulcer peptic activ sau în antecedente sau hemoragie (două sau mai multe episoade distincte, diagnosticate, de ulcer sau sângerări),pacienți cu insuficiență hepatică severă, insuficiență renală severă sau insuficiență cardiacă severă, pacienți cu hemoragie cerebrovasculară sau alte hemoragii active, tulburări de coagulare sanguină sau diateză hemoragică, pacienți cu tulburări hematopoietice de etiologie neprecizată,pacienți cu deshidratare severă (provocată de vărsături, diaree sau aport insuficient de lichid), utilizarea în trimestrul trei de sarcină. În timpul celui de-al treilea trimestru de sarcină,utilizare ibuprofenului este interzisă. Alăptarea - ibuprofenul și metaboliții săi pot trece în concentrații mici în laptele matern. Condiții de prescripție - se eliberează fără rețetă. Informația completă despre produs este indicată în prospectul pacientului și rezumatul caracteristicilor preparatului Brufen Rapid în Republica Moldova de la 07.04.2021 nr.26419 și 26420. Producător-Geltec Private Limited, SR. No. 24, 26/3, 27/2, Yadavnahalli, Attibele, Hosur Rd, Bengaluru, Karnataka 562107, India. În prealabil eliberării și consumului, este necesară studierea aprofundată a fișei de însoțire și descrierii scurte a preparatului.

Bibliografie: 1. Rezumatul caracteristicilor produsului medicamentos Brufen Rapid 600 mg în granule efervescente, Brufen Rapid 400 mg sub formă de capsule moi. 2. IQVIA MIDAS database: Q3 2022 Release 3. Schachtel, B P et al. "A placebo-controlled model to assay the onset of action of non prescription-strength analgesic drugs." Clinical pharmacology and therapeutics vol. 55,4 (1994): 464-70. doi:10.1038/clpt.1994.56t 4. Sharma N.K. et.al .Primary Dental Care. 1994.1(1): 5-8 5. Tablets vs. Capsules: Pros, Cons, and How They Differ, https://www.healthline.com/health/capsule-vs-tablet , ultimul acces 24.02.2023. Pentru informație suplimentară puteți să Vă adresați la SRL "Abbott Ucraina": 01010, or. Kiev, str. Moskovskaia, 32/2, BC "Senator". Tel.: +380 44 498 60 80, fax: +380 44 498 60 81. Pentru publicare în reviste specializate, destinate specialiștilor în medicină și farmacie, instituțiilor medicale.

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