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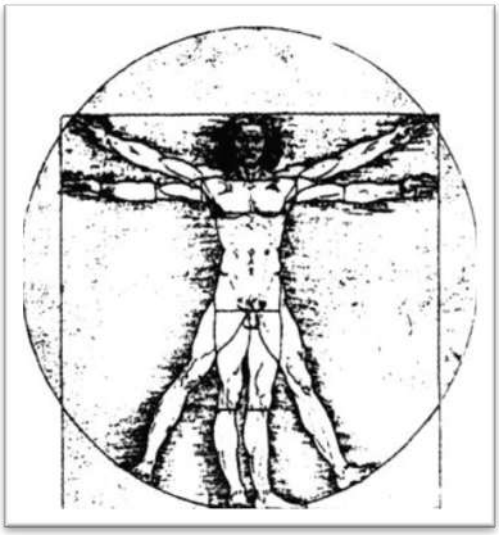

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ORIGINAL ARTICLE

COMPARISON OF TWO SURGICAL TECHNIQUES OF ACROMIO-CLAVICULAR DISLOCATION GRADE III OR IV TREATMENT - A RETROSPECTIVE STUDY OF FUNCTIONAL RESULTS FOLLOWING SURGERY AT THE CLINIC OF TRAUMATOLOGY-SKOPJE IN THE PERIOD OF 2015–2018

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ABSTRACT

Introduction: Acromioclavicular (AC) dislocation is an injury occurring most commonly in younger male athletic patients. Dislocation to the acromioclavicular joint is the result of a direct force applied on the dome of the acromion and the most common mechanism of injury is a direct fall on the top of the shoulder. The aim of our study was to compare two surgical methods of AC dislocation grade III or IV with Tight Rope system and HOOK plate and functional results afterwards. In our study we used Dash (Disabilities of the Arm, Shoulder and Hand) and VAS (Visual Analogue Scale) scores.

Materials and Methods: During the period of 2015- 2018 48 patients were treated with type III (21 patients) or IV AC dislocation (27 patients) with female to male ratio 0.6 (f:m=18:30) at the University Clinic of Traumatology. Inclusion criteria were applied to all patients. We used three radiographic views: AP view, true axillary view and stress view of both sides of the AC joint and CC ligament. Two surgical methods were performed, Tight Rope technique and fixation with HOOK plate.

Results: Dash **(**Disabilities of the Arm, Shoulder and Hand**)** and VAS (Visual Analogue Scale) scores were used for postoperative evaluation of the functional outcome. The DASH chart was used as an indicator of the impact of an impairment on the level and type of disability. The results demonstrated better scores in the group treated with Tight Rope technique.

Conclusion: Tight Rope technique proved to be more effective in treating acute AC dislocations (Rockwood type III or IV) with a high degree of Excellency and good functional results. HOOK plate osteosynthesis is more adequate for higher grade of AC diastasis.

Keywords: AC diastasis, HOOK plate, Tight Rope, shoulder surgery.

INTRODUCTION

Acromioclavicular (AC) dislocation is an injury specific for younger male athletic patients. Dislocation to the acromioclavicular joint is the result of a direct force applied of the dome of the acromion and the most common mechanism of injury is a direct fall on the top of the shoulder. The clavicle sits on top of the first rib, which blocks further downward displacement of the clavicle. As a result, if the clavicle is not fractured, the acromioclavicular and coracoclavicular ligaments are ruptured.

The overall incidence is 3 to 4 per 100 000 in the general population, with 25% to 52% occurring during sporting activities [1,2]. Less frequent mechanism of injury is fall on an outstretched hand or elbow, where the traumatic force may be transmitted to the shoulder through the whole length of the arm.

The acromioclavicular capsular ligaments provide stability of the acromioclavicular joint in the anteroposterior direction, while coracoclavicular (CC) provide vertical stability.

Sage and Salvatore proposed a classification of acromioclavicular joint injuries depending on the severity of damage to the respective structures. Although many surgeons still use three grades of severity of separation, Rockwood *et al.* have subclassified these injuries further into types I through VI. Treatment of grade I and II AC joint dislocations can be performed conservatively [3]. However, surgical intervention is required for patients with grades III (especially individuals who are workers with heavy manual occupations, overhead throwing athletes, etc.) and IV–VI (because of their common characteristics including instability in the horizontal and vertical direction of both due to AC ligament and coracoclavicular (CC) ligament disruption). There is still a lack of consensus on whether to operate or not type III AC joint dislocations. There are different types of fixation devises, varying from locking plates to different types of button systems including even the old reliable Zuggurtung fixation [4, 5]. The aim of our study was to evaluate the surgical outcome of two different types of operative treatments of AC dislocation grade III or IV, which are Tight Rope system and HOOK plate fixation.

MATERIALS AND METHODS

At the University Clinic of Traumatology, during the period of 2015 to 2018 year, 48 patients were treated with type III (21patients) and IV AC dislocation (27 patients). Female to male ratio was 0.6 (f:m=18:30). The median age was 35 years (in the range of 18 to 54 years) and most of the patients were physically active individuals. With Tight Rope methods 20 patients were operated with grade 3 to grade 4 ratio 3 (gr.3:gr.4=15:5). With HOOK plate osteosynthesis 28 patients were treated with grade 3 to grade 4 ratio 0, 27 (gr.3:gr.4=6:22). All patients were operated within 48 hours after trauma event.

Inclusion criteria were:

1. Acute AC joint and type III or IV dislocation according to the Rockwood classification,
2. No prior history of shoulder injuries and related operations,
3. Type III cases were enrolled into the study if the distal end of the clavicle was located more or equal to 75 to 100% of its articular surface width in the radiographs and if painful palpation and protuberance shape of the clavicle during shoulder anterior raising in clinical diagnosis existed.
4. Isolated injury.

Exclusion criteria were:

1. Elderly, obese, sedentary patients.
2. Acute AC joint trauma with reducible joint, little apparent deformity and type I or II dislocation according to the Rockwood classification,
3. Polytraumatised patients.

Minimum follow up period was 12 months. To determine the type of injury of the shoulder and the presence of Acromioclavicular (AC) dislocation, three radiographic views were used: AP view (with 10 degrees cranial tilt of the beam or Zanca view), true axillary view in the supine position and stress view of both sides of the AC joint. Anteroposterior, lateral, and axial views are standard views were taken for the shoulder. Weighted X-rays can help differentiate type I from type II injuries and more importantly type II from occult type III injuries.

Tight Rope method

With this surgical technique were operated 20 patients, from who with grade 3 AC diastasis were diagnosed 15 patients and with grade 4 AC diastasis 5 patients. The stability of the shoulder and AC joint reduction was evaluated when the patient was placed in the beach chair position. All examinations were performed under local or general anesthesia. For controlling the infection, three doses of cephalosporin (second-generation) were administered in all cases. At first, the injured upper limb of the patient was prepped and draped in the normal sterile condition. For this purpose, the anatomical landmarks such as anterior portion of the acromion, distal clavicle, and coracoid process were used to determine the skin incision. Skin incision was made 4-6 over the tip of coracoid process and was elongated proximally to the anterior edge of clavicle bone. Then the incision line was expanded on the subcutaneous tissue down to the deltoid muscle. After blunt splitting of deltoid muscle, with ease was exposed base of coracoid process. Then the interval between coracoid process and distal part of the clavicle was split. The tissue was dissected medially and laterally by a curved soft tissue elevator. First step is preparing of drill hole on base coracoid process and is starting with placing a 2.4 mm guide pin. Then, the guide pin was carefully over drilled by a 4.5 mm drill. Because under coracoid process are places soft tissue elements like subclavian artery it is advised when over drilling starts to put some kind of protection on the underside of coracoid process like curettage. In the next step to drill holes are drilled on the superior surface of the clavicle on the same manner as it was drilled on the coracoid process except it is over drilled with 3.5 mm drill. First hole is placed on the middle of the clavicle (the center of the distance between the anterior and posterior borders from the superior surface of the clavicle) 2.5 cm medially of acromioclavicular joint, second hole is placed 1.5 to 2.5 cm medially. Before placing of Tight Rope device anterior superior attachment of deltoid muscle on the clavicle should be bluntly detached (after placement of the Tight Rope device with sutures it is attached again thru 3 small holes on the anterior border of the clavicle drilled with 2.4 mm guide pin). At first, the Tight Rope device was inserted into the hole of the coracoid process than thru the holes on the clavicle (Fig.1) the clavicle and then through the coracoid hole by a button inserter.

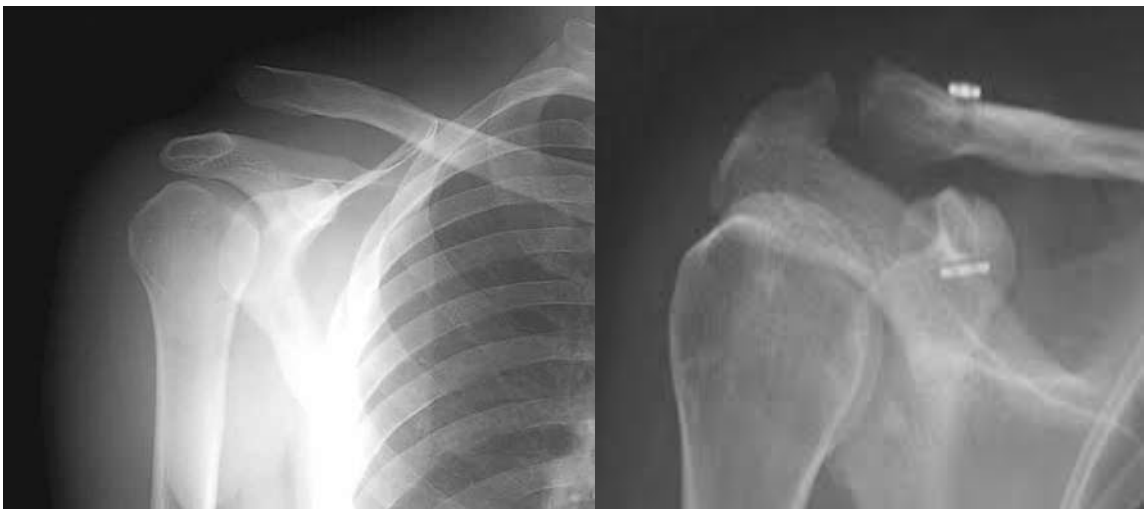

Fig. 1. M, 32 Y, a construction worker, fall on the shoulder while cycling, AC dislocation grade III. DASH score 0; VAS score 2.

After this step AC joint reduction was performed in the anatomical position under pressure using the fluoroscopic visualization by pulling on the sutures on the buttons on the clavicle until clavicle sits on the same place before the traumatic incident. According to post-operative protocol, shoulder mobilization was placed 3 to 4 weeks post operatively.

HOOK plate osteosynthesis

With this surgical technique were operated 20 patients, from who with grade 3 AC diastasis were diagnosed 6 patients and with grade 4 AC diastasis 22 patients. This procedure is also performed with the patient in beach chair position. For controlling the infection, three doses of cephalosporin (second-generation) were administered for all patients. The patient was under general anesthesia. A 4-6 cm skin incision was made over the lateral end of clavicle and extending over acromion process. After identifying acromioclavicular joint with sterile 18-gauge needle (this allows the surgeon a clear determination of the size and integrity of the distal clavicle fragment) a HOOK locking plate with 3 holes is applied to all patients with locking screws while reduction was achieved under fluoroscope control. According to post-operative protocol, shoulder mobilization was placed 3 to 4 weeks post operatively.

RESULTS

All patients were evaluated preoperatively and postoperatively with Dash (Disabilities of the Arm, Shoulder and Hand) and VAS (Visual Analogue Scale).The Disabilities of the Arm, Shoulder and Hand (DASH) outcome measure is a 30-item, self-report chart designed to assess the patient's health status during the previous week. Dash question chart is divided on 3 groups of questions:

1. First group is focused on performing different physical activities on patients with arm, shoulder and hand problems (21 items),
2. Second group is focused on the severity of symptoms of pain, activity-related pain, tingling, weakness and stiffness (five items) and
3. Third one is focused on quality of life after surgery which are the impact of the problem on social functioning, work, sleep and self-image (four items).

Each item has five response options (no difficulty, mild difficulty, moderate difficulty, severe difficulty, unable). The scores are then used to calculate a scale score ranging from 0 (no disability) to 100 (most severe disability). The DASH question chart is used as an indicator of the impact of impairment on the level and type of disability. The results in this study were in favor Tight Rope surgical technique (Table 1 and Table 2).

Table 1. Results of Dash **(**Disabilities of the Arm, Shoulder and Hand) evaluation 3 months after surgery

DASH SCORING	Tight Rope	HOOK plate
No difficulty	5	8
Mild difficulty	13	15
Moderate difficulty	2	4
Severe difficulty	/	1
Unable	/	/

Table 2. Results of Dash (Disabilities of the Arm, Shoulder and Hand) evaluation 1 year after surgery

DASH SCORING	Tight Rope	HOOK plate
No difficulty	14	17
Mild difficulty	6	9
Moderate difficulty	/	2
Severe difficulty	/	/
Unable	/	/

VAS pain scale is also by question chart that measures response of different type of physical activity to physical pain and response is quantified as following: no pain (0–4), mild pain (5-44), moderate pain (45–74), and severe pain (75–100).

According to our results, majority of the patients did not suffer greater pain one year after surgery. However, the results of the DASH score and VAS scale were better in the group treated with Tight-Rope method, which is presented on Table 5 and Table 6.

Table 3. VAS (Visual Analogue Scale) 3 months after surgery

VAS SCORING	Tight Rope	HOOK plate
No pain	6	7
Mild pain	11	15
Moderate pain	3	4
Severe pain	/	2

Table 4. VAS (Visual Analogue Scale) 1 year after surgery

VAS SCORING	Tight Rope	HOOK plate
No pain	15	13
Mild pain	5	13
Moderate pain	/	2
Severe pain	/	/

DISCUSSION

The major advantage of the Tight Rope system is that once placed, it does not need another operation for extracting. Another advantage is that it maintains reduction, and yet allows for normal physiologic movement of the joint. Complications include displacement of the endo-buttons (thought to be due to the use of a larger drill bit to create the portal), and posterior displacement of the clavicle with respect to the anterior edge of the acromion, which is best evaluated on axillary views and abrasions on the clavicle from the superior buttons that lead to dull chronic pain on the top aspect of the clavicle. Martetschläger F. *et al.* in their study elaborated that this technique has major advantages in comparation to Hook plate, but the experience and skill of the surgical team should be adequate and specialized [6]. Complications of HOOK plate are acromial bony erosion (Fig. 2), shoulder impingement and even rotator cuff damage.

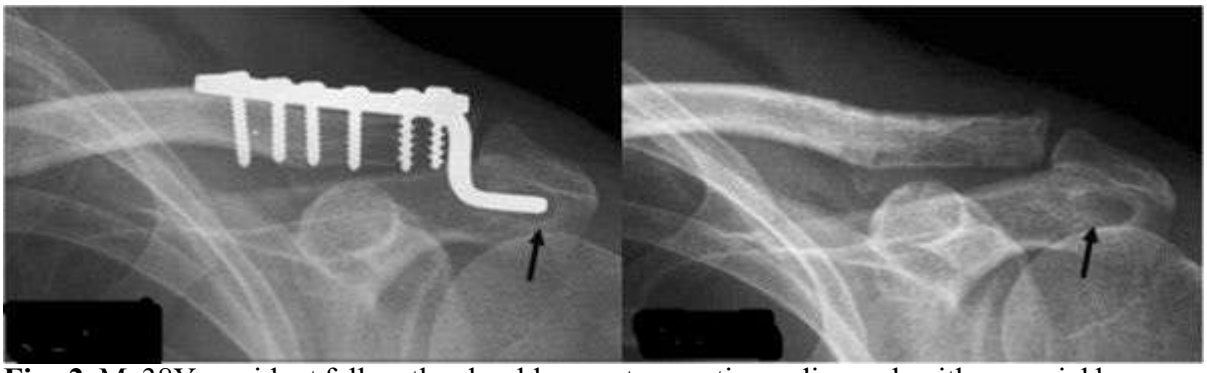

Fig. 2. M, 38Y, accident fall on the shoulder, post-operative radiograph with acromial bony erosion.

Also, due to acromial erosion the plate should be removed 4 to 6 months after implantation, so additional surgery was a necessity. Babhulkar A. *et al*. in a study published in 2014 year, determined that Hook plate caused eroding of acromion as early as 32 days after surgery. Also, the percentage of arthritis od acriomioclavicular joint was very high, above 50% of the cases. [7]

The results of our retrospective study showed better results in the group treated with the Tight Rope technique for the functional score, as well as for the pain score. Similar results were demonstrated in other published data, which clearly explains the advantage of the Tight Rope technique compared to the conventional HOOK plate [8,9].

CONCLUSION

Tight Rope technique proved to be more effective in treating acute AC dislocations (Rockwood type III or IV) with a high degree of excellency and good functional results. HOOK plate osteosynthesis is more adequate for higher grade of AC diastasis.

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ORIGINAL ARTICLE

DIAGNOSING ABDOMINAL OBESITY IN WOMEN WITH CUT – OFF POINT VALUES OF THE ESTIMATED CENTRAL OBESITY INDEX DETERMINED WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY

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ABSTRACT

Introduction: Dual-energy X-ray absorptiometric (DXA), central obesity index (COI) and estimated COI (eCOI) are useful diagnostic DXA test procedures of extreme central, abdominal obesity in Cushing's syndrome (CS) and non CS abdominally obese women, and determination of their diagnostic cut-off point values (CPV) is very important.

Materials and methods: COI and eCOI values were determined in 3 groups, each consisting of 18 women: 1st group of CS, 2nd group of obese women (O) not different according to their age and Body Mass Index (BMI) with CS and 3rd group of non-obese healthy women (C) with normal BMI. COI_1 and $eCOI_1$ CPV were used to best differentiate CS and O. COI_2 and $eCOI_2$ CPV were used to best differentiate CS and O with C. Their diagnostic accuracy (DG), sensitivity (S) and specificity (SP) were determined.

Results: COI and eCOI values were significantly different among the 3 groups. COI_1 CPV of 0.9 best differentiated CS from O with DG of 70% and sensitivity of 90% but $eCOI_1$ CPV of 0.92 differentiated them with DG of 75% and S of 100%.

COI_2 CPV of 0.82 best differentiated C from O with DG of 82.14% and SP of 88.89% as well as $eCOI_2$ CPV of 0.84 differentiated them for DG of 75% and SP of 80%. COI_2 CPV of 0.82 and $eCOI_2$ 0.84 best differentiated CS from C in both cases for DG of 92.86% and SP of 88.89%.

Conclusion: Cut-off point values of COI_1 and COI_2 as well as $eCOI_1$ and $eCOI_2$ are very important diagnostic test procedures in discovering abdominal and normal body fat distribution. Determined $eCOI_1$ and $eCOI_2$ cut-off point values are especially very useful diagnostic screening tests of body fat distribution in everyday routine clinical praxis during spine and hip bone mineral content assessment.

Keywords: Dual-energy X-ray absorptiometry, abdominal obesity, central obesity indexes, cut-off point values.

INTRODUCTION

Obesity and especially central body fat distribution (BFD) are known risk factors for cardiovascular and metabolic diseases. Android obesity in CS and in non CS abdominally obese women with the metabolic syndrome, which is predominantly visceral, intra-abdominal, is more predictive of adipose-related comorbidities than gynecoid obesity, which has a relatively peripheral (gluteal) distribution [1, 2]. Effective methods for assessing abdominal, visceral fat are important to investigate its role for the increased health risks in obesity [3, 4, 5]. For this reason the evaluation of body composition and BFD is clinically important. Dual-energy X-ray absorptiometry (DXA) is considered to be a gold standard for assessment of bone health and body composition, because of its reliability, precision, and the fact that it is based on a three-compartment model [6, 7].

DXA is used to quantify abdominal fat mass and enables precise, accurate body composition and body fat distribution assessment and determines central obesity index values.

Body fat distribution was determined with DXA and central obesity index (COI), which was calculated as a ratio of the android to gynoid tissue percent fat, and differentiated significantly Cushing's syndrome (CS) from suspect obese. It was discovered that COI index could be used as a screening test procedure and diagnostic criterion of extreme central, abdominal obesity in CS and in non CS abdominal obese [8]. Very recently, it was confirmed that DXA indexes COI and estimated COI (eCOI) discovered extreme central body fat distribution in CS women, differentiated them significantly and precisely from the group of non-obese healthy women (C), and O, and both of them could be used as diagnostic DXA indexes of extreme central, abdominal obesity in CS and non CS abdominally obese women in DXA body composition and fat distribution assessment. That study concluded that the determination of eCOI with DXA method is reliable, more practical and faster, with lower radiation and is more acceptable compared to COI, and it can be a routine screening procedure for body composition and body fat distribution assessment during regular spine and hip scans for osteoporotic risk assessment. Body fat distribution determined with COI is used in scientific studies and is not necessary to be performed in clinical body fat distribution examinations [9]. Also, to date cut-off point values of COI and eCOI have not been provided in order to precisely confirm abdominal obesity in CS and non CS obese.

The aim of this study was to determine cut-off point values of DXA indexes of central, abdominal obesity, COI_1 and $eCOI_1$, which best differentiate CS and the group of obese women as well as C. Also, it was important to determine normal COI_2 and $eCOI_2$ cut-off point values, which best differentiate group C and O and exclude abdominal obesity.

MATERIALS AND METHODS

This transversal study was organized and realized at the University Clinic of Endocrinology, Diabetes and Metabolic Disorders, Faculty of Medicine, Ss Cyril and Methodius University in Skopje. DXA assessment of body composition and body fat distribution was performed in three groups of women, each consisting of 18 subjects: 1st group of Cushing's syndrome (CS), with clinically confirmed CS with Body Mass Index (BMI) (30.25±5.64 kg/m^2) and age of 43.58±13.58 years, 2nd group of obese women, matched with CS according to their BMI (29.8±4.08 kg/m^2) and age (40.4±12.05 years) and the 3rd group of healthy women with normal BMI (21.59±1.35 kg/m^2) and age (40.09±12.72 years). All examined women were not different according to their age. CS and O were also not different according to their BMI. BMI in C was significantly lower compared to CS and O.

CS had not received any treatment at the time of the assessment and had typical signs and symptoms of CS including extreme central obesity. Anthropometric, DXA, hormonal and metabolic parameters confirmed CS diagnosis. O and C had a stable weight for at least several months before being included in the study.

All investigated women have signed an informed consent to be included in this study and have been treated according to the Declaration of Helsinki.

DXA assessment in this study was performed with DXA System Lunar DPX-NT, which uses an enCore Windows-XP Professional OS computer. For body composition measurements the entire body of each subject was scanned. During DXA scan, the subjects were in a supine position while the x-ray scanner performed a series of transverse scans, measured at 1-cm intervals from the top of the head to the bottom of the toes. Also, standard spine and hip scans were estimated. COI values were determined during body composition assessment in total body scans as a ratio of android (A) tissue percent (%) fat (A-Tf%) and gynoid (G) Tf% (G-Tf%), COI= A/G-Tf%.

Using the scanned tissue data from the standard spine and hip scans estimates of the eA-Tf% and eG-Tf% values of the lumbar vertebral spine (L_2-L_4) and proximal femur were determined, eAndroid/eGynoid Tfat% ratio was performed and eCOI = eA/eG - Tf% was calculated.

Cut-off point values of DXA indexes of central, abdominal obesity COI_1 and $eCOI_1$ were determined to best differentiate CS with confirmed abdominal obesity from O, healthy women matched for age, menopausal status, and BMI. Also, cut-off point values of DXA indexes of normal body composition and fat distribution COI_2 and $eCOI_2$ that best differentiate C and O as well as C and CS and exclude abdominal obesity were determined.

Cut-off point values (CPV) were determined for all four DXA indexes and their sensitivity (S), specificity (SP), positive and negative predictive value (PPV and NPV) and diagnostic accuracy (DG) were evaluated in the following way:

• Sensitivity (true positive rate) is the probability that a test result will be positive; there is extreme visceral obesity when the CS disease is present.
• Specificity (true negative rate) is the probability that a test result will be negative; there is no extreme central body fat distribution when the disease is not present in C and O.
• Positive predictive value (PPV) is the proportion of those with a positive test result (extreme central body fat distribution) who actually have a disease (CS).
• Negative predictive value (NPV) is the proportion of those with a negative test result (without extreme central obesity) who do not have a disease (C and O).
• Diagnostic accuracy (effectiveness) was expressed as a proportion of correctly classified subjects (true positive rate + true negative rate) among all subjects.

Statistical analyses were performed using statistical software program SPSS for Windows, version 19.0. Variables were presented as means ± standard deviations (SD). P values <0.05 were considered to be statistically significant. Differences among the groups were evaluated by performing an analysis of variance (ANOVA) for normally distributed parameters. Correlation coefficients were determined by Pearson's product moment.

RESULTS

Central obesity index values determined during body composition assessment in total body scans as a ratio of android to gynoid tissue % fat and their S, SP, PPV, NPV and DG were compared to their estimated COI values determined during standard spine and hip scans.

Table 1. Significance of the difference between COI and eCOI values in CS, O and C

	COI	eCOI	p-value
CS	1.07±0.15	1.07±0.09	NS
O	0.88±0.12	0.91±0.12	NS
C	0.64±0.15	0.72±0.098	NS

CS – Cushing 's syndrome; O – obese; C – non obese.

COI and eCOI values were not significantly different in all examined groups. COI values in the three examined groups (0.82±0.23) highly significantly positively correlated with eCOI values (0.86±0.18) ($P<0.0001$).

Table 2. Significance of the difference of COI and eCOI values between the Cushing 's syndrome and obese women

Variable	Cushing's Syndrome	Obese women	p-value
COI	1.07±0.15	0.88±0.12	0.005
eCOI	1.07±0.09	0.91±0.12	0.001

Table 3. Significance of the difference of COI and eCOI between the Cushing 's syndrome and non-obese women

Variable	Cushing Syndrome	Non obese women	p-value
COI	1.07±0.15	0.64±0.15	0.0001
eCOI	1.07±0.09	0.72±0.098	0.0001

Table 4. Significance of the difference of COI and eCOI values between the obese women and non-obese women

Variable	Obese women	Non obese women	p-value
COI	0.88±0.12	0.64±0.15	0.0001
eCOI	0.91±0.12	0.72±0.098	0.0001

COI and eCOI values were significantly different among the three groups. They were highest in CS compared to O and C confirming the most expressed central, abdominal obesity in CS.

Table 5. S, SP, PPV, NPV and DG of COI_1 and $eCOI_1$ cut-off point values in differentiation of CS and O

	COI_1>0.9	$eCOI_1$>0.92
Sensitivity (%)	90	100
Specificity (%)	50	50
PPV (%)	64.29	66.67
NPV (%)	83.33	100
DG (%)	70	75

COI_1 - Central obesity index 1; $eCOI_1$ - Estimated central obesity index 1;
PPV – Positive predictive value; NPV – Negative predictive value; DG - Diagnostic accuracy.

COI_1 cut-off point value of 0.9 and $eCOI_1$ value of 0.92 best differentiated extreme central, abdominal, visceral body fat distribution in CS women from O. COI_1 values higher than 0.9 and eCOI values higher than 0.92 confirmed extreme central, abdominal body fat distribution in CS and also indicated central, abdominal body fat distribution in non CS obese women.

Table 6. S, SP, PPV, NPV and DG of COI_2 and $eCOI_2$ cut-off point values determined in differentiation of O and C as well as CS and C

Variable	COI_2<0.82		$eCOI_2$<0.84	
	CS-C	O-C	CS-C	O-C
S (%)	100	70	100	70
SP (%)	88.89	88.89	88.89	80
PPV (%)	83.33	77.78	83.33	77.78
NPV (%)	100	84.21	100	72.73
DG (%)	92.86	82.14	92.86	75

COI_2 - Central obesity index 2; $eCOI_2$ - Estimated central obesity index 2; CS – Cushing's Syndrome; O – obese; C – non obese; PPV – Positive predictive value; NPV – Negative predictive value; DG - Diagnostic accuracy.

COI_2 cut-off point value of 0.82 and $eCOI_2$ cut-off point value of 0.84 best differentiated group C from group O, as well as group C from group CS. Values of COI_2 lower than 0.82 and $eCOI_2$ values lower than 0.84 indicated normal body fat distribution in group C. Diagnostic accuracy of COI_2 and $eCOI_2$ was higher in differentiation of C and CS compared to C and O.

DISCUSSION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have adverse effects on health, leading to reduced life expectancy and/or increased health problems [10, 11]. Very recently, the World Obesity Federation argued that "obesity was considered as a chronic, relapsing, progressive, disease process" that requires intervention [12]. Obese subjects have higher percentage of fat mass from the total body mass compared to non obese [4]. However, obese individuals differ not only according to the degree of excess fat which they store, but also in the regional distribution of the fat within the body. The main characteristic of the metabolic syndrome is increased body weight, and particularly central, abdominal obesity as well as dyslipidemia [13, 14]. Obese individuals with metabolic syndrome have an especially higher risk for stroke, coronary artery disease, hypertension, cardiovascular disease - related mortality and type 2 diabetes, fatty liver and several cancers, and a number of other chronic diseases, when compared with individuals of normal weight and BFD [13, 15].

It was discovered with DXA that BMI increase in healthy women was associated with a more pronounced abdominal body fat distribution, indicating substantially higher risk for development of metabolic and cardiovascular complications especially in postmenopausal women [16, 17, 18, 19]. DXA also measures and monitors body composition changes in obese patients undergoing weight loss. Measurements of body composition and body fat distribution have provided a research tool to study the metabolic effects of aging, obesity, and various diseases such as CS [6, 19, 20, 21].

Cushing's syndrome is associated with weight gain and extreme central, visceral, abdominal obesity. Increased central fat mass is characteristic of active CS. In Jebb's study [22] Cushing disease patients had higher visceral versus total adipose tissue ratios, suggesting that glucocorticoids play a pivotal role in the pathogenesis of central obesity [23]. The first study concerning the measurements of body composition in CS using DXA and CT was published by Wajchenberg et al. [24]. Patients with CS had no increase in total body fat or the trunk region, but had a higher intra-abdominal fat area compared to obese subjects [25].

Patients with CS had less than a twofold increase in subcutaneous fat and greater than a fivefold increase in intra-abdominal fat compared with values in healthy subjects. Garrapa et al. [26] evaluated body composition and fat distribution measured by DXA in women with CS and compared them with healthy control women matched for age, menopausal status, and BMI and discovered that trunk fat mass percentage was significantly higher in CS and leg fat mass was not significantly different between the two groups. Fat mass was higher and lean body mass was lower in CS. These findings suggest that fat in different body compartments responds differently to disease processes and that DXA can be used to measure these changes [26, 27, 28, 29].

The differences of the body composition and body fat distribution in women with CS with confirmed extreme abdominal, visceral obesity in comparison with healthy obese control women matched for age, menopausal status, and BMI were evaluated with DXA. It was discovered that total and regional fat mass, tissue mass, lean body mass (LBM) values did not differentiate CS and O significantly and it was concluded that the determinations of the relationships of their regional values had to be done.

Also, it was shown with DXA scans of the entire body that the ratios of the not significantly different central (abdominal) and peripheral regional parts of the body, significantly and precisely differentiated the patients with CS and non CS obese, and confirmed extreme central body fat distribution in CS. DXA enabled determination of body fat distribution as well as central obesity index COI, which is an indicator of central, abdominal obesity, and was calculated as a ratio of the android to gynoid tissue percent fat. COI differentiated significantly CS from suspect obese and it was discovered that it could be used as a screening test procedure and diagnostic criterion of extreme central, abdominal obesity in CS and in non CS [6, 8].

COI was discovered as a useful method for assessing body fat distribution which is in a positive relation with abdominal (central) obesity, and the metabolic syndrome. It was concluded that CS patients were discovered as a gold standard of extreme central, visceral, abdominal body fat distribution [23], and that some of these DXA indexes of extreme central, abdominal body fat distribution in CS could also be used as a gold standard for abdominal obesity in non CS. It was confirmed that COI as a ratio of android to gynoid tissue % fat is an indicator of central, abdominal obesity, which is the main characteristic of the metabolic syndrome. It was established that eCOI measurements of the estimated android to gynoid tissue fat percent values were reliable and comparable to measured COI values. Determination of eCOI was more practical, faster, with lower radiation and was more acceptable; moreover, spine and hip bone mineral content were determined at the same time. Total body composition measurements are used in scientific studies and are not necessary to be done in body fat distribution examination in clinical practice. It indicated the need of eCOI values determination during regular spine and hip DXA measurements for body fat distribution assessment instead of total body composition assessment with COI values. High significance of the COI and eCOI correlation with android tissue percent fat and its estimated value was detected in comparison with the correspondent gynoid values, confirming COI positive association with central, abdominal fat and tissue mass, and abdominal fat distribution. COI (A/G tissue % fat) and eCOI values were significantly different among the three groups, and were not significantly different in each group. In that study cut-off point values of COI and eCOI were not provided in order to precisely confirm abdominal obesity in CS and non CS obese [9]. Because of that, the aim of this study was to determine cut-off point values of DXA indexes of central, abdominal obesity COI_1 and $eCOI_1$ that best differentiated CS and O as well as C. Also, it was important to determine normal COI_2 and $eCOI_2$ cut-off point values that best differentiate group C from CS and O and exclude abdominal obesity.

In this study, COI and eCOI values were not significantly different in all examined groups. COI correlated highly significantly positively with eCOI values ($p<0.0001$). COI and eCOI values were significantly different among the three groups. They were highest in CS compared to O and C confirming the most expressed central, abdominal obesity in CS.

COI_1 cut-off point value of 0.9 best differentiated CS from O with DG of 70% and $eCOI_1$ value of 0.92 differentiated them for DG of 75%. CS and O were differentiated with high sensitivity of 90% for COI_1 and 100% for $eCOI_1$. High sensitivity was needed in order to precisely discover central, abdominal body fat distribution. COI_1 was not superior compared to $eCOI_1$ in diagnosing the visceral, abdominal obesity.

COI_2 cut-off point value of 0.82 best differentiated O from C for DG of 82.14% and $eCOI_2$ value of 0.84 differentiated them for DG of 75%. Specificity was 88.89% for COI_2 and 80% for $eCOI_2$. COI_2 cut-off point value of 0.82 and $eCOI_2$ value of 0.84 best differentiated CS from C in both cases for DG of 92.86% and specificity of 88.89%. High specificity and DG were important in differentiating these groups because cut-off point values of these indexes of normal body fat distribution are needed to exclude abdominal obesity and confirm normal body fat distribution. COI_2 and $eCOI_2$ cut-off point values differentiated better CS and C compared to O and C because of the more exaggerated abdominal body fat distribution in CS compared to O and especially to C.

Also, BMI increase is associated with more pronounced abdominal obesity. These two indexes are good screening procedures and their normal COI value lower than 0.82 and eCOI lower than 0.84 confirmed normal body fat distribution and more sophisticated DXA indexes of total body composition assessment are not needed.

CONCLUSION

COI and eCOI values were not significantly different in all examined groups and COI correlated highly significantly positively with eCOI values. COI and eCOI values were highest in CS compared to O and C confirming the most expressed central, abdominal obesity in CS.

Total body composition measurements are used only in scientific studies and are not necessary to be done in clinical routine of body fat distribution assessment, but $eCOI_1$ determination could be used as a clinical screening routine analysis of abdominal obesity as practical, fast, with lower radiation and very acceptable; moreover, spine and hip bone mineral content are determined at the same time.

It can be concluded that COI_1 and COI_2 as well as $eCOI_1$ and $eCOI_2$ were confirmed as useful procedures in discovering abdominal and normal body fat distribution. Determined cut-off point values of $eCOI_1$ and $eCOI_2$ are very important in routine clinical praxis as useful screening test procedures in discovering abdominal and normal body fat distribution during spine and hip bone mineral content assessment as more practical, faster, with lower radiation and more acceptable diagnostic procedures compared to the total body composition assessment.

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ORIGINAL ARTICLE

DESCRIPTIVE ANALYSIS OF CLINICAL AND DEMOGRAPHIC DATA OF SELECTED GROUP OF PATIENTS WITH PULMONARY EMBOLISM

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ABSTRACT

Pulmonary embolism is a relatively common clinical entity accompanied with a high mortality and is a perplexing diagnostic and therapeutic problem. Current research indicates that pulmonary embolism has a multifactorial and complex pathogenesis. Genetic factors have been under extensive research during the past two decades.

The aim of this study was to present a descriptive analysis of demographic and clinical data obtained thus far from 31 patients with documented pulmonary embolism.

In our patient group, almost half of the patients were non-smokers and all denied alcohol consumption. More than 80% of the patients had no history of previous pulmonary embolism and no thrombophlebitis, but nearly two thirds of all patients had deep vein thrombosis. A history of acute myocardial infarction existed in about 6.5% of patients, as well as ischemic stroke. Arterial hypertension was present in about one-third of patients, dyslipidemia in 42%, and type 2 diabetes in approximately 13%. Only one patient had an anamnestic data for chronic renal disease, while none had a history of hepatic disease.

The results of the analysis of demographic-clinical data of patients are concordant with the results of the previously published studies.

Keywords: pulmonary embolism, thromboembolism, gene polymorphism.

INTRODUCTION

Pulmonary embolism is a relatively common clinical entity with a high mortality rate and is a perplexing diagnostic and therapeutic problem. It is a disorder of the pulmonary circulation when a thrombus becomes lodged in a lung artery and its branches. It is considered to have a multifactorial and complex pathogenesis, and over the last twenty years genetic factors have been extensively investigated.

Cardiovascular risk factors (deep vein thrombosis, history of hypertension and cardio- and cerebrovacular events) are significantly associated with pulmonary embolism. Nevertheless, many patients with serious risk factors such as massive and long-term deep vein thrombosis do not experience pulmonary embolism, whereas in some patients it appears due to some trivial reasons. These discrepancies strongly suggest the influence of the genetic factors, especially because the risk of repeated pulmonary embolism is higher in subjects with familiar history of this clinical entity.

Until now a large number of genetic investigations of certain thrombophilias more often associated with pulmonary embolism have been made, including mutations and polymorphisms of the genes of Factor V Leiden, prothrombin (PTM G20210A), methylentetrahydrofolate reductase (MTHFR C677T and A1298C), protein C, protein S and antithrombin III (AT-III) [1]. Previously published studies have shown a statistical correlation with specific single nucleotide polymorphisms and with other genetic alterations (deletions, insertions, etc.) in certain genes with prevalence in pulmonary embolism as well as with therapeutic response to anticoagulant therapy [2,3,4].

The aims of the ongoing doctoral disseration thesis are to determine the correlation between the three selected gene polymorphisms with the prevalence, demographic, clinical and laboratory parameters in patients with pulmonary embolism and to determine the eventual existance of combined, epistatic influence of the three polymorphisms on the mentionted parameters.

Furthermore, the aim is to determine the potential usage of the three polymorphisms in identification of patients with a high risk of pulmonary embolism, prediction of the therapeutic response and their prognostic value.

This study presentsthe descriptive analyses of the so far obtained data from 31 patients.

MATERIALS AND METHODS

The study was planned to include about 60 patients with clinically confirmed pulmonary embolism, selected according to inclusion and exclusion criteria. All included patients underwent CT angiography as a method of choice for detection of embolus in the main, lobar or segmental pulmonary arteries. The control group consisted of samples of about 30 healthy controls that were matched by sex and age with the group of patients with pulmonary embolism, but with no anamestic data about thrombotic conditions (deep vein thrombosis, recurrent episodes of thrombophlebitis and pulmonary embolism) and no family history of these entities in the close family members as well as no documented cardiovascular and cerebrovascular conditions and hepatic or kidney diseases.

For each patient data were obtained with regard to selected demographic characteristics (sex, age, level of education, type of profession, smoking history, alcohol consumption, dyslipidemias, hypertension, familial history of thrombotic conditions, usage of oral contraceptive drugs, etc.), laboratory values (thrombocytes, coagulation status, D-dimers, troponin, etc.) as well as clinical data (comorbidities and risk factors, selected values of CT angiography of pulmonary arteries, echocardiography, Doppler ultrasound of blood vessels, calculated scores according to Wells and/or revised Genevascales, data about treatment, therapeutic response and clinical outcome).

Data were taken only from patients who, after being given a detailed explanation about the procedures, aims and their rights, signed volunatarily their written informed consent. Also, information obtained from patients was kept confidential and in line with the directives of the Law on personal data protection. The study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje.

The statistical descriptive analyses in this study were made by using the software packages XLSTAT 2016 and Microsoft Excel 2016.

RESULTS

Data and samples of a total of 31 patients with pulmonary embolism were collected. Analyses of clinical and demographic data of these patients are herein presented.

Sex and age structure of the 31 patients is presented in Tables 1 and Figure 1.

Table 1. Sex distribution of patients

Sex	n	%
Men	13	41.94
Female	18	58.06
Total	31	100.00

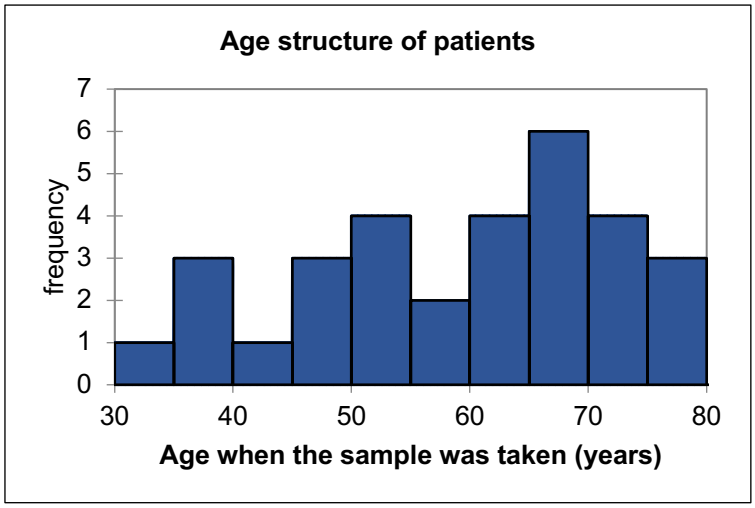

Fig. 1. Histogram of the age structure of patients.

The presented results clearly show that female subjects predominated in the group of patients with almost 60% as well as older patients. The largest number of patients was aged between 65 and 70 years, although the mean age was 58 years.

Descriptive statistical analyses of the data regarding body weight, height and BMI index of patients are presented in Figure 2.

To present the data in figures the so-called *box-and-whiskers* type of figures was used.

The fence of each rectangular box corresponds to the first quartile (25th percentile), and the upper fence defined as the third quartile (75th percentile) of the values encompasses 50% of all measurements. The horizontal line through each rectangular box presents median (geometrical mean) while the red symbol denotes arithmetic means. Vertical positive and negative segments pertain to distribution of maximum and minimum deviations in the measurements corrected with the third and first quartiles, respectively.

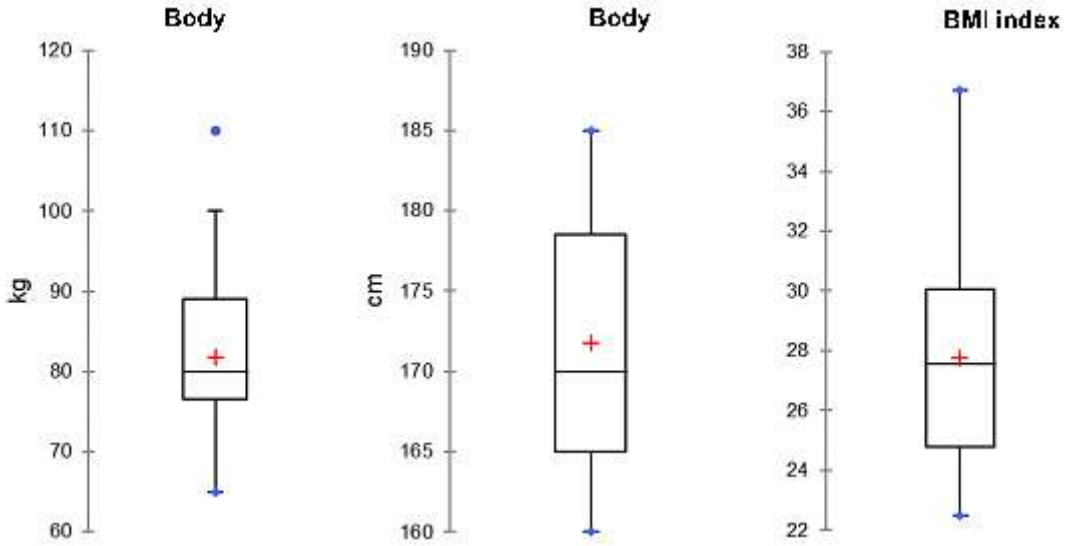

Fig. 2. Body weight, height and BMI index of patients.

Data about the place of residence, level of education and type of profession of patients are presented in Table 4.

Table 4. Social data of patients

Data	**n**	**%**
Place of residence		
city	22	70.97
village	9	29.03
Level of education		
primary	2	6.45
high	17	54.84
university	12	38.71
Type of profession		
farmer	4	12.90
worker	14	45.16
clerk	13	41.94

Preliminary segment of the demographic and clinical data that were relevant for pulmonary embolism in the examined patients is presented in Table 5.

Table 5. Relevant demographic and clinical data of patients

Data	n	%
History of smoking		
non-smokers	15	48.39
rarely	1	3.23
moderately	10	32.26
intensively	5	16.13
Alcohol consumption		
does not drink	31	100.00
rarely	0	0.00
moderately	0	0.00
intensively	0	0.00
Previous pulmonary embolism		
no	26	83.87
yes	5	16.13
Anamnesis of deep vein thrombosis		
no	19	61.29
yes, once	12	38.71
yes, several times	0	0.00
Anamnesis of thrombophlebitis		
no	31	100.00
yes, once	0	0.00
yes, several times	0	0.00
Anamnesis of AMI		
no	29	93.55
yes, once	2	6.45
Yes, several times	0	0.00
Anamnesis of ischemic brain insult		
no	29	93.55
yes, once	2	6.45
yes, several times	0	0.00
Anamnesis of hepatic diseases		
no	31	100.00
yes	0	0.00
Anamnesis of renal diseases		
no	30	96.77
yes	1	3.23
Arterial hypertension		
no	10	32.26
yes	21	67.74
Dyslipidemia		
no	13	41.94
yes	18	58.06
Type 2 diabetes		
no	27	87.10
yes	4	12.90

As it can be seen from the presented results, almost half of the patients said they were non-smokers and none of them consumed alcohol. More than 80% of them gave no anamnestic data about previous pulmonary embolism; none of them had thrombophlebitis, but almost two thirds of all patients had deep vein thrombosis.

History of acute myocardial infarction was noted in about 6.5% of patients and the same percentage of patients had ischemic brain stroke. About one third of patients had arterial hypertension, 42% had dyslipidemia and type 2 diabetes about 13%. Anamnestic data about chronic kidney disease was given by one patient only, while none had hepatic diseases. The results of the descriptive analysis with regard to thrombocytes count in the acute phase of pulmonary embolism in the group of examined patients are illustrated in Table 6.

Table 6. Levels of D-dimers, thrombocyte count, and scores according to Wells and revised Geneva scale of pulmonary embolism

Data	Levels			
	Average	**Minimum**	**Maximum**	**Standard deviation**
D-dimers (ng/mL)	884.81	260.00	2220.00	554.41
Thrombocytes (x 10^9/L)	331.81	128.00	617.00	109.40
Wells scale	6.21	4.00	8.60	1.01
Revised Geneva scale	7.87	6.00	11.00	1.45

DISCUSSION

This paper presents the preliminary descriptive analysis of data obtained for 31 patients with pulmonary embolism. The collected demographic and clinical data and their descriptive statistical analysis would select the parameters that are going to be used for comparison and determination of the genetic correlation with the molecular parameters or polymorphisms. Data stratification point out which demographic-clinical parameters are not present in all patients or are found in a very small number of patients, and hence, can help in selection of parameters that will enable a qualitative statistical comparison with the frequencies of genotypes and alleles of the examined polymorphisms.

Quantitative measurements of the risk factors for adequate interpretation of the degree of clinical suspicion of pulmonary embolism were assessed according to the Wells score for pulmonary embolism and Revised Geneva score for pulmonary embolism. Low level of D-dimers (under 500 ng/ml) has a highly negative predictive value and in combination with the objective clinical evaluation was done prior to the procedures of thrombi visualization because of the reduction in the radiation degree and expenses savings. The increased level of D-dimers has low specificity and does not confirm the diagnosis of pulmonary embolism, but initiates the need of additional diagnostic examinations.

Cardiovascular risk factors, including arterial hypertension and anamnesis for existence of deep vein thrombosis were found in a larger number of examined patients with pulmonary embolism and these results were in agreement with other studies [5].

By completing the anticipated molecular analysis for determination of the genetic polymorphisms we expect to affirm the existence of their correlation with the key parameters of pulmonary embolism, and eventually with the therapeutic response. Thus, in addition to the basic science, in future they can be applied as biomarkers when selecting patients at high risk, selecting therapy for pulmonary embolism and in prognostic aims [6].

CONCLUSION

The results obtained have shown that cardiovascular risk factors were significantly present in the group of patients with pulmonary embolism. They included arterial hypertension, dyslipidemia and history of deep vein thrombosis as well as smoking and older age. The increased level of D-dimers had low specificity and it did not confirm the diagnosis of pulmonary embolism, but indicated the need of additional diagnostic investigations. By completing the anticipated molecular analyses for determination of genetic polymorphisms, their association with the key parameters of pulmonary embolism is to be expected, along with the eventual therapeutic response.

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ORIGINAL ARTICLE

ENDOMETRIAL THICKNESS ASSESSED BY TRANSVAGINAL ULTRASOUND AS A PREDICTOR OF THE RISK OF ENDOMETRIAL CANCER AND ATYPICAL ENDOMETRIAL HYPERPLASIA IN ASYMPTOMATIC POSTMENOPAUSAL PATIENTS

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ABSTRACT

Introduction: Endometrial cancer (EC) is the most common gynecological malignancy in the developed world. It is estimated that 320000 new cases are diagnosed annually, accounting for up to 6% of all newly diagnosed malignant neoplasms. In spite of the associated controversies, transvaginal sonography and measurement of endometrial thickness are well-accepted, standard procedures in many gynecological office visits to date.

Objective: The study aim was to determine the diagnostic performance of endometrial thickness measured by transvaginal sonography in diagnosing endometrial cancer and atypical endometrial hyperplasia in asymptomatic postmenopausal patients.

Materials and methods: The databases of the Department of gynecological oncology at the University Clinic of Gynecology and Obstetrics in Skopje, in the period January – December 2015 were searched to identify asymptomatic postmenopausal patients undergoing endometrial sampling due to increased endometrial thickness.

Results: A total of 268 patient records that met the criteria were identified. The prevalence of endometrial cancer and atypical endometrial hyperplasia in the study were 5.2% and 2.2%, respectively. Endometrial thickness was a statistically significant independent predictor of the presence of endometrial cancer and atypical endometrial hyperplasia ($p<0.001$). The ROC curve analysis in our study had an AUC of 0.8 and identified a cut-off level to be ≥10mm which was associated with a sensitivity of 85.7%, specificity of 60.6%, PPV of 10.7% and NPV of 98.7% for the detection of endometrial cancer.

Conclusion: The proposed cut-off of ≥10mm for discriminating between "normal" and "pathological" endometrial thickness is clinically reasonable and of moderate diagnostic value. However, the cut-off value does not achieve the required high sensitivity with clinically acceptable low false positive rates. Nevertheless, transvaginal sonography for measuring endometrial thickness can be used to exclude pre-malignancy or malignancy in asymptomatic postmenopausal women with risk factors because of its low false negative rate.

Keywords: Endometrial cancer, atypical endometrial hyperplasia, endometrial thickness, asymptomatic postmenopausal patients.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world [1, 2]. It is estimated that 320000 new cases are diagnosed annually, accounting for up to 6% of all newly diagnosed malignant neoplasms.

In the Republic of North Macedonia, endometrial cancer is the second most common malignant neoplasm in women (after breast cancer), with an estimated 400 new patients diagnosed annually [1], and a corresponding age-standardized incidence rate of 24.3 per 100000 women.

Postmenopausal bleeding and endometrial thickening in postmenopausal women, assessed by transvaginal ultrasonography (TVUS) are indicative of an endometrial cancer diagnosis [3, 4]. The majority of patients with endometrial cancer present with postmenopausal bleeding and patients with postmenopausal bleeding have a 5-10% chance of having endometrial cancer. Nevertheless, up to 15% of endometrial cancers may manifest in asymptomatic patients [5].

It is well established [6, 7] that patients presenting with postmenopausal bleeding and an endometrial thickness >4mm should undergo further diagnostic evaluation to confirm or exclude endometrial cancer, while patients with endometrial thickness ≤4mm can be reassured without the need for further investigation, as the risk of endometrial cancer in that subgroup is less than 1%. [8]. Consensus is lacking, however, for asymptomatic patients with increased endometrial thickness. This is mostly due to the fact that a universal cut-off value for endometrial thickness that warrants histologic sampling has not been established. A number of studies have used low thresholds (less than 10mm) for endometrial thickness, which provided adequate sensitivity, while simultaneously steeply increasing the number-to-treat needed to diagnose a patient with endometrial cancer [9-12]. Smith-Bindman et al. [13] published data from a theoretical cohort of 10000 postmenopausal women designed to determine an optimal endometrial thickness threshold that should be considered abnormal in the absence of vaginal bleeding. The authors found that the risk of endometrial cancer in patients with postmenopausal bleeding id 7.4% if the endometrium is thicker than 5mm and 0.07% if the endometrium is thinner than the cut-off. A threshold of 11mm yielded the same stratification of endometrial cancer risk in patients in the asymptomatic group; the risk of endometrial cancer was 6.7mm in patients with endometrial thickness > 11mm and 0.002% in patients with endometrial thickness ≤11mm. Furthermore, the authors concluded that using the conventional 4mm cut-off to define an abnormal transvaginal endometrial ultrasonography in asymptomatic patients would increase the number of false-positive results beyond the number of true-positive test results [13]. Jacobs et al. published data of a nested case-control study [14] of a large cohort of patients undergoing transvaginal ultrasonography in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) with a primary endpoint of detecting endometrial cancer and atypical endometrial hyperplasia. The authors demonstrated that endometrial thickness of 10 and 20 mm were associated with a number-to-treat needed to detect endometrial cancer/atypical endometrial hyperplasia (AEH) of 17 and 6, respectively. The authors concluded that the role of population screening for endometrial cancer remains uncertain and that the burden of diagnostic procedures and false-positive results can be reduced by limiting screening to a high-risk group of patients.

In spite of the associated controversies, transvaginal sonography and measurement of endometrial thickness are well-accepted, standard procedures in many gynecological office visits to date [15]. Given that the histological evaluation of asymptomatic patients with endometrial thickness >4mm is relatively common in our institution, we conducted a retrospective analysis to better define the rationale for further diagnostic evaluation of asymptomatic postmenopausal patients with increased endometrial thickness. The objective of the study was to determine the diagnostic performance of endometrial thickness measured by transvaginal sonography in diagnosing endometrial cancer and atypical endometrial hyperplasia in asymptomatic postmenopausal patients.

MATERIALS AND METHODS

This retrospective study was conducted at the Department of gynecologic oncology at the University clinic of gynecology and obstetrics, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia. We searched the Clinic's patient registers from January until December 2015 for eligible postmenopausal patients that were admitted at our outpatient department for endometrial sampling. Exclusion criteria were: (1) postmenopausal bleeding; (2) endometrial thickness less than 4mm; (3) history of endometrial hyperplasia/cancer; (4) history of tamoxifen use; (5) incomplete patient records; (6) current hormone replacement therapy use; (7) known history of hereditary non-polyposis colon cancer (HNPCC); (8) inadequate endometrial sample for histopathology. The following data were extracted from the patient records: age at sampling, age at menarche, age at menopause, number of pregnancies, parity, history of hypertension and diabetes, endometrial thickness and the histology from the endometrial sampling. Post-menopause was defined as the absence of periods for at least 12 months prior to the sampling. Each patient had a transvaginal ultrasonography scan done by the attending physician no more than 14 days prior to the sampling, in accordance with the standard operating procedures of the Department. The endometrial thickness was measured in the sagittal plane, using a conventional transvaginal probe in a standardized fashion. The endometrial sampling was done by dilatation and curettage (D&C) with or without previous hysteroscopic evaluation (at the discretion of the attending). All histological samples were evaluated at the Department of histopathology at the University clinic for oncology and radiotherapy, University Ss. Cyril and Methodius, Skopje, Republic of North Macedonia.

The data was anonymized and entered into a database. The statistical analysis was carried out using the SPSS statistical software package version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). A value of $p<0.05$ was considered statistically significant. Standard descriptive statistics were done and data was displayed using frequencies, percent, mean and standard deviation (SD), where appropriate. Based on the histopathology reports, two separate binary outcome variables were created: presence of EC and presence of EC/AEC, based on the argument that there is a high rate of underdiagnosed malignancies and/or progression to cancer in patients with atypical endometrial hyperplasia [16, 17]. To check for possible confounders, we carried out logistic regressions to test the association of the analyzed factors with the outcomes.

The diagnostic performance of endometrial thickness was evaluated by plotting receiver-operating characteristic (ROC) curves and calculated the area under the curve (AUC). Sensitivity, specificity and Youden's index were calculated for each point on the ROC curves. The point with the highest Youden index was selected as the optimal cut-off in our data. We then calculated the positive and negative predictive value (PPV and NPV) of the test using the selected cut-offs and calculated the relative risk of the patient having EC or EC/AEC when the endometrium thickness is above the cut-off.

RESULTS

We identified a total of 268 patient records that fitted the inclusion and exclusion criteria. Table 1 summarizes the relevant demographic and clinical patient characteristics. All patients were Caucasian. The mean age at the moment of endometrial sampling was 61.2±7.1 years, with an interval of 11.3±7.2 years from menopause to sampling. Patients had an average of 36.8±4.6 reproductive years, 3.2±1.8 pregnancies and 2.1±1 delivery. Eleven (4.1%) of the patients were nulligravidae, and fourteen (5.2%) od the patients were nulliparous.

Over half of the patients (162, 60.4%) had hypertension and 31 (11.9%) had diabetes. The mean endometrial thickness was 9.3mm with a standard deviation of 3.2mm and a range from 5-23mm.

Table 1. Summary of the relevant demographic and clinical patient characteristics

Parameter	No. patients n=268
TVUS Endometrial thickness (mm), mean±SD [range]	9.3±3.2 [5-23]
Age at sampling (years), mean±SD	61.2±7.1
Age at menarche (years), mean±SD	13.1±1.5
Age at menopause (years), mean±SD	50±4.4
Interval from menopause to sampling (years), mean±SD	11.3±7.2
No. of reproductive years	36.8±4.6
Number of pregnancis	3.2±1.8
Number of deliveries	2.1±1
Nulligravidity, n (%)	11 (4.1%)
Nulliparity, n (%)	14 (5.2%)
Hypertension, n (%)	162 (60.4%)
Diabetes, n (%)	32 (11.9%)

A vast majority of the evaluated patients had benign endometrial lesions (248 patients or 92.6%), 6 patients (2.2%) had atypical endometrial hyperplasia and 14 patients (5.2%) had endometrial cancer. The various histological findings are outlined in detail in Table 2.

Table 2. Distribution of histological diagnoses in the studied population

	n (%)
Atrophic endometrium	135 (50.4%)
Endometrial polyp	70 (26.1%)
Other benign conditions (endometritis, leiomyoma...)	28 (10.5%)
Simple endometrial hyperplasia	13 (4.8%)
Complex endometrial hyperplasia without atypia	2 (0.8%)
Complex endometrial hyperplasia with atypia	6 (2.2%)
Endometrial cancer	14 (5.2%)
Endometroid adenocarcinoma	8 (2.9%)
Mixed serous and mucinous adenocarcinoma	4 (1.5%)
Serous adenocarcinoma	1 (0.4%)
Clear cell carcinoma	1 (0.4%)

The univariate logistic regression revealed a statistically significant association of endometrial thickness with both the presence of EC ($p<0.001$) and EC/AEC ($p<0.001$). The other factors were not significantly associated (Table 3).

The distribution of benign endometrial lesions, atypical endometrial hyperplasia and EC for different levels of endometrial thickness are shown in Figure 1. As expected, the proportion of premalignant/malignant endometrial lesions increases with increased endometrial thickness.

Table 3. Univariate logistic regression for determining the association between the clinical parameters and EC or EC/AEH in the studied population

Parameter	p (EC)	p (EC/AEH)
Endometrial thickness	<0.001	<0.001
Age at sampling	0.14	0.39
No. of reproductive years	0.92	0.3
Interval from menopause to sampling	0.18	0.78
Nulligravidity	0.07	0.19
Nulliparity	0.14	0.33
Hypertension	0.8	0.67
Diabetes	0.58	0.78

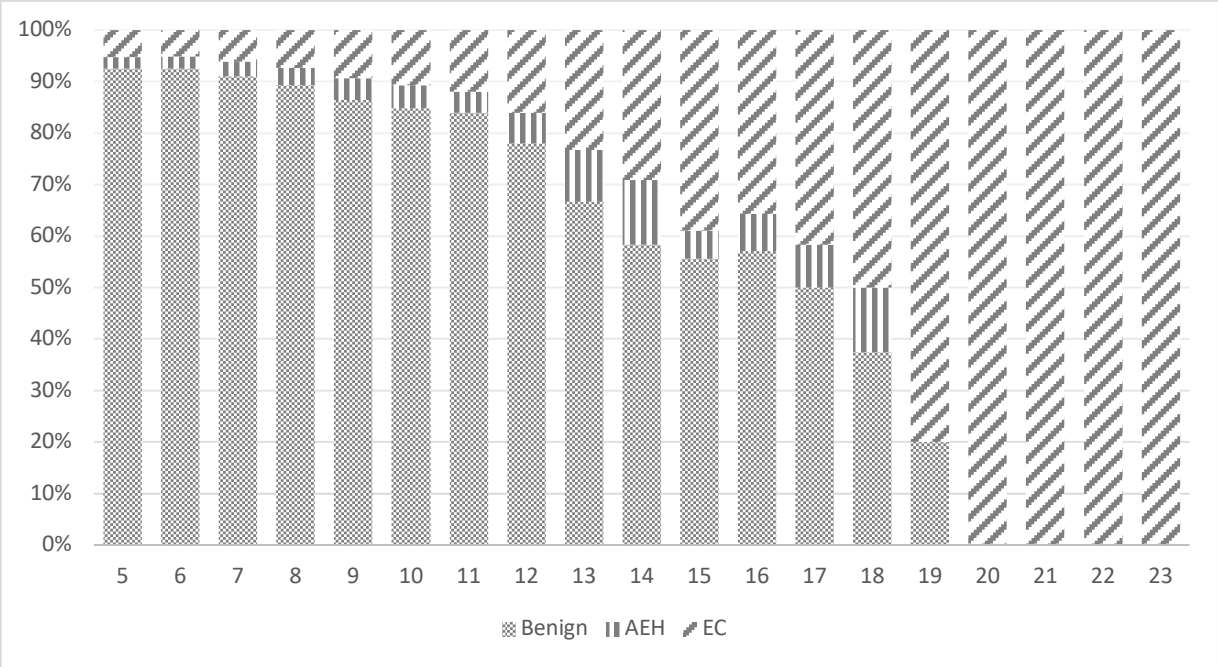

Fig. 1. Distribution of benign endometrial lesions, AEH and EC for different levels of endometrial thickness.

In order to evaluate the diagnostic performance of endometrial thickness measured by transvaginal sonography for the detection of EC and EC/AEC, two ROC curves were plotted (Figures 2 and 3). The AUC was 0.8 for detection of both EC (95%CI 0.66-0.94, p<0.001) and EC/AEC (95%CI 0.7-0.91, p<0.001).

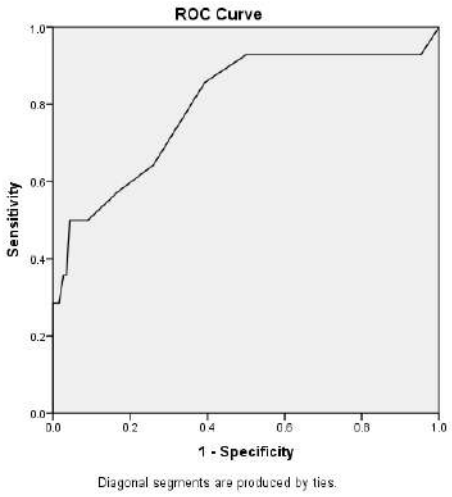

Fig. 2. ROC curve curve of transvaginal ultrasound measurement of endometrial thickness in asymptomatic postmenopausal for the detection of EC.

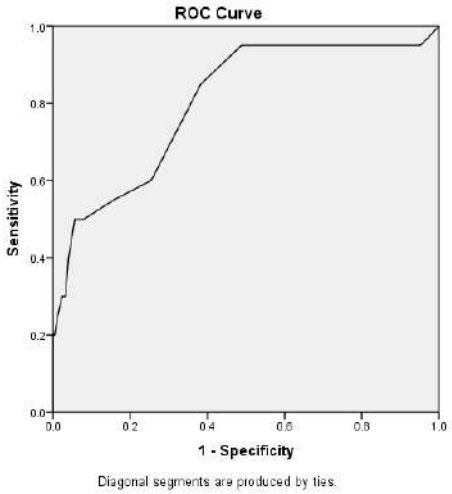

Fig. 3. ROC curve curve of transvaginal ultrasound measurement of endometrial thickness in asymptomatic postmenopausal for the detection of EC/AEH.

The results for the diagnostic performance of different cut-off points for endometrial thickness in the detection of EC and EC/AEH are summarized in Table 4 and 5 respectively. The optimal cut-off points for endometrial thickness measured by transvaginal sonography (selected using the Youden index) in our series was 10mm, yielding a sensitivity of 85.7% and 85%, specificity of 60.6% and 61.7%, PPV of 10.7% and 15.2% and NPV of 98.7% and 98.1% for the detection of EC and EC/AEH, respectively. The risk for EC and EC/AEH using the cut-off was 10.7% and 15.2%, respectively.

Table 4. Diagnostic performance for different cut-offs for endometrial thickness in the detection of EC in asymptomatic postmenopausal patients

Cut-off point (mm)	Sensitivity	Specificity	PPV	NPV	Youden index
≥5	93.3%	4.5%	5.2%	92.3%	-2.2%
≥6	92.9%	4.7%	5.1%	92.3%	-2.4%
≥7	92.9%	22.0%	6.2%	98.2%	14.9%
≥8	92.9%	35.4%	7.3%	98.9%	28.3%
≥9	92.9%	50.0%	9.3%	99.2%	42.9%
≥10	85.7%	60.6%	10.7%	98.7%	46.3%
≥11	64.3%	74.0%	12.0%	97.4%	38.3%
≥12	57.1%	83.5%	16.0%	97.2%	40.6%
≥13	50.0%	90.9%	23.3%	97.1%	40.9%
≥14	50.0%	93.3%	29.2%	97.1%	43.3%
≥15	50.0%	95.7%	38.9%	97.2%	45.7%
≥16	35.7%	96.5%	35.7%	96.5%	32.2%
≥17	35.7%	97.2%	41.7%	96.5%	33.0%
≥18	28.6%	98.4%	50.0%	96.2%	27.0%
≥19	28.6%	99.6%	80.0%	96.2%	28.2%
≥20	28.6%	100.0%	100.0%	96.2%	28.6%

Table 5. Diagnostic performance for different cut-offs for endometrial thickness in the detection of EC/AEH in asymptomatic postmenopausal patients

Cut-off point (mm)	Sensitivity	Specificity	PPV	NPV	Youden index
≥5	95.2%	4.6%	7.5%	92.3%	-0.1%
≥6	95.0%	4.8%	7.5%	92.3%	-0.2%
≥7	95.0%	22.6%	9.0%	98.2%	17.6%
≥8	95.0%	36.3%	10.7%	98.9%	31.3%
≥9	95.0%	51.2%	13.6%	99.2%	46.2%
≥10	85.0%	61.7%	15.2%	98.1%	46.7%
≥11	60.0%	74.6%	16.0%	95.9%	34.6%
≥12	55.0%	84.3%	22.0%	95.9%	39.3%
≥13	50.0%	91.9%	33.3%	95.8%	41.9%
≥14	50.0%	94.4%	41.7%	95.9%	44.4%
≥15	40.0%	96.0%	44.4%	95.2%	36.0%
≥16	30.0%	96.8%	42.9%	94.5%	26.8%
≥17	30.0%	97.6%	50.0%	94.5%	27.6%
≥18	25.0%	98.8%	62.5%	94.2%	23.8%
≥19	20.0%	99.6%	80.0%	93.9%	19.6%
≥20	20.0%	100.0%	100.0%	93.9%	20.0%

DISCUSSION

The study present data from 268 asymptomatic postmenopausal women with endometrial thickness >4mm. The prevalence of EC and AEH in the study were 5.2% and 2.2%, respectively. Endometrial thickness was a statistically significant independent predictor of the presence of endometrial cancer and atypical endometrial hyperplasia ($p<0.001$).

Schmidt et al. reported a similar prevalence of endometrial cancer (4.9%) in a prospective study of asymptomatic postmenopausal women [18], while Giannella et al. [19] in a similar prospective study found the prevalence of EC to be 2.1%. Data on the prevalence of EC in asymptomatic postmenopausal women with thickened endometrium from retrospective studies varies widely form 1.3-13.2% [4, 20, 21].

Transvaginal sonographic scans are frequently performed for various clinical indications. Therefore, the accidental finding of thickened endometrium in asymptomatic postmenopausal women is a relatively common occurrence and represents a diagnostic conundrum in many primary gynecologic practices. Historically, the cut-off points for endometrial thickness that warrant patient refferal for further histological (often invasive) evaluation have been the same as the ones used for patients with postmenopausal bleeding (i.e. 5mm) [9-12].

While the data from patients with postmenopausal bleeding points toward clear clinical recommendations, a cut-off point for endometrial thickness in asymptomatic postmenopausal women that would provide acceptable trade-off between cancer detection and unnecessary biopsies prompted by an incidental finding has remained debatable.

The ROC curve analysis in our study had an AUC of 0.8 and identified a cut-off level for EC/AEH to be ≥10mm which was associated with a sensitivity of 85.7% and 85%, specificity of 60.6% and 61.7%, PPV of 10.7% and 15.2% and NPV of 98.7% and 98.1% for the detection of EC and EC/AEH, respectively. Using that cut-off as the basis for the decision for endometrial sampling would "miss" 2 cases of EC and 1 case of AEH which account for 15% of all premalignant/malignant endometrial lesions in our series, but would also reduce the number of D&C procedures by 58%.

Kasraeian et al. [22] conducted a prospective observational cohort study on 259 asymptomatic postmenopausal. When using 5 mm as a cut-off point to detect EC, the authors reported sensitivity of 100 %, specificity of 84.4 %, PPV of 2.43 %, and NPV of 100 %, and an AUC of 0.853, indicating moderate accuracy. A recent metanalysis conducted by Alcazar et al on aggregated data from 4751 women had a prevalence of EC and/or AEH of 2.4%. The authors stated that the relative risk of EC and/or AEH was 2.59 with endometrial thickness ≥11 mm. They also observed high heterogeneity between studies (I2: 57.3%, P = 0.016). Two large cohort studies, the theoretical cohort by Smith-Bindman et al. [13] and the UKCTOCS study [14], suggest that choosing a cut-off value well above the one used for patients with postmenopausal bleeding, i.e. >10-12mm seems to be a viable strategy to decrease the needed number-to-treat for the early detection of EC cases. Our data compares favorably with these series. It should be noted, however, that the risk for EC in our series is higher (10.7%) than the risk for EC published in the theoretical cohort (6.7%) and the UKCTOCS study (5.9%). The UKCTOCS study has achieved sensitivity of 84.3 % and specificity of 89.9 % with a cutoff of 6.75 mm, but only after stratifying the study population into a low-risk and high-risk groups, using a logistic regression model [14]. The authors have concluded that the burden of diagnostic procedures and false-positive results can be reduced by limiting sonographic screening for EC to a high-risk population.

Conversely, Breijer et al. in their systematic review including 32 studies with data of over 11100 patients, concluded that endometrial thickness should not be used as a screening tool for EC or AEH in asymptomatic postmenopausal women [10]. Similarly, Yasa et al. in a retrospective study of 276 consecutive asymptomatic perimenopausal women found that endometrial thickness does not seem to be an effective diagnostic tool for the early detection of EC because it had a low diagnostic performance in asymptomatic postmenopausal women. Furthermore, a retrospective study on 2673 consecutive patients found that 44% of office hysteroscopies aimed at diagnosing EC were not indicated.

It can be argued that, although of low yield, pre-symptomatic diagnosis of EC might impact the course of the disease and improve survival in these patients. In a series of 313 EC patients (190 symptomatic and 123 asymptomatic with suspicious endometrium detected by ultrasound), Gerber et al. [25] found no prognostic advantage for screened patients compared to symptomatic patients with bleeding episodes lasting less than 8 weeks prior to diagnosis. Duration of bleeding had also no impact on EC prognosis in a study of 304 EC patients [26]. In a large group of 133 asymptomatic and 410 symptomatic patients with EC, the authors found that symptoms were not related to stage or age at diagnosis and the presence or absence of symptoms was not associated with improved survival.

Survival advantage from EC diagnosis in asymptomatic postmenopausal patients was also demonstrated in a large Israeli Oncology Group study adequately powered for survival measures [28].

The authors stated that there was no difference between asymptomatic EC patients and EC patients with postmenopausal bleeding in the 5-year recurrence-free survival (79.1% vs. 79.4%; p = 0.85), disease-specific survival (83.2% vs. 82.2%; p = 0.57), or overall survival (79.7% vs. 76.8%; p = 0.37). Therefore, operative hysteroscopy/curettage procedures in asymptomatic patients with sonographically diagnosed endometrial polyps or thick endometrium are rarely indicated and should be reserved for patients whose ultrasonographic findings demonstrate significant change over time [28].

Our study is not free of limitations. First its retrospective nature being subject to selection bias due to unmeasured confounders. Second, the study was conducted on a gynecologic-oncology department in a tertiary referral center. Although referral for histological diagnosis of asymptomatic thickened endometrium in the Republic of North Macedonia is liberal, it can be assumed that not all women with thickened endometrium were referred. Therefore, it can be hypothesized that due to the selection bias of a register study, we overestimated the risk for cancer compared to a general screening situation. Additionally, our cohort comprised of an above-average number of patients with comorbidities that were referred to our department they could not be treated safely in a secondary care center. The fact that many of those comorbidities are also risk factors for endometrial cancer might explain the high percentage of diagnosed cancers in our study. Lastly, we only evaluated the endometrial thickness and disregarded any additional data from the ultrasonography reports, such as specific morphology and/or Doppler evaluation, which could have revealed more information.

CONCLUSION

This retrospective cohort analysis found that an increased endometrial thickness, measured by transvaginal sonography, is a significant and independent risk factors for the presence of EC in asymptomatic postmenopausal women, which is in line with previously published data from the UKCTOCS trial and a theoretical cohort. No association was found between EC and related conditions such as diabetes and hypertension. The proposed cut-off of ≥10mm for discriminating between “normal” and “pathological” endometrial thickness is clinically reasonable and of moderate diagnostic value. However, the cut-off value does not achieve the required high sensitivity with clinically acceptable low false positive rates. Nevertheless, transvaginal sonography for measuring endometrial thickness can be used to exclude pre-malignancy or malignancy in asymptomatic postmenopausal women with risk factors because of its low false negative rate. Additionally, it is a preoperative diagnostic tool that might provide the surgeon with additional information important for the choice of surgical procedures, or as an alternative to endometrial sampling in postmenopausal women who cannot undergo invasive procedures. A well-designed large prospective study is required to reach consensus about the optimum endometrial thickness cut-off to initiate an investigation in asymptomatic postmenopausal women with incidental finding of thickened endometrium.

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ORIGINAL ARTICLE

EPIDEMIOLOGY, TREATMENT, AND COMPLICATIONS OF CROUP SYNDROME IN CHILDREN

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ABSTRACT

Introduction: Croup syndrome is an urgent pediatric condition. It is characterized by the abrupt onset, most commonly at night, of a barking cough, that is usually accompanied by inspiratory stridor, hoarseness and respiratory distress resulting from upper-airway obstruction. This is the most common reason why parents are upset and immediately seek medical help.

Objective: This study aimed to evaluate the frequency, treatment, and possible complications of croup syndrome in children hospitalized at our institute.

Materials and methods: In our retrospective study we examined 56 pediatric cases with croup syndrome that were hospitalized in our Institute and we analyzed gender and age, the season in which we had the most frequent hospitalizations of children with croup syndrome, as well as treatment and possible complications after completion of croup symptoms. Period of examination was one year.

Results: Mean age at diagnosis of children with croup was 26,5 ±2.6 months (range from 45 days to 8 years). As well the world statistics we got a larger number of hospitalized boys with croup syndrome, rather than girls (ratio 2,3:1). Regarding the period of the year, the autumn period was dominant. As far as the treatment, we noticed significant number of children with moderate to severe croup syndrome that required in-patient care. All of them received nebulized adrenalin as well as parenteral corticosteroid. The average duration of the hospitalizations that occurred in our unit for close monitoring and semi-intensive care was 5 days (1-14d). Antibiotics were used in 71% (n=40). Most common comorbidity was pneumonia and bronchopneumonia (14,2%, n=8). None of the children was of need of intubation and referral to intensive care unit.

Conclusion: Our one-year research has documented considerable number of children with the necessary hospitalization, as many as 10% of hospitalized children in our Institute were due to moderate to severe croup syndrome. The sex, the age of the children as well as the season are most often in line with world statistics. We are noticing high percent of hospitalized patients with moderate croup. There is evident discrepancy between the use of antibiotics and its duration in our practice in comparison with other reports. These observations lead to reassessment of the hospitalization criteria as well as more rational use of antibiotics.

Keywords: Croup syndrome, intensive care, pediatric, treatment.

INTRODUCTION

Infections of the upper respiratory tract are the most common acute infectious pathology in childhood. Croup syndrome is an urgent pediatric condition and is characterized by the abrupt onset, most commonly at night, of a barking cough, hat is usually accompanied inspiratory stridor, hoarseness, and respiratory distress resulting from upper-airway obstruction.

The disease has an autumn-winter season predominance [1] and affects children from 6 months to 3 years of age, peaking at 2 years of age, which is determined by the anatomical features of the upper respiratory tract (URT) in infants and young children. The male to female ratio is 3: 2 [2].

Croup is usually caused by viruses, which are detected in up to 80 percent of patients. Various presentations of croup are based on the causative virus. Parainfluenza virus (types 1 to 3) is the most common etiology (50 to 75 percent of patients with croup). Of the three types, parainfluenza type 1 is the most common. Although parainfluenza type 3 virus infections often occur in young children, croup develops in only a small percentage of those exposed. Other viruses that cause croup are enterovirus, human bocavirus, influenza A and B viruses, respiratory syncytial virus, rhinovirus, and adenovirus. Measles has been reported rarely in patients with croup where the population is inadequately vaccinated. Bacterial causes are also rare and include diphtheria and Mycoplasma pneumonia [3, 4].

Pathogenesis is associated with generalized inflammation of the dilated pits with swelling of the mucosa and hypersecretion of the mucous glands. The subglottic area narrows, leading to obstruction of the respiratory tract.

Westley Croup Score, is the most widely used clinical score, and its validity and reliability have been well demonstrated. However, RCTs included in the review use a variety of croup scores. **Mild croup:** occasional barking cough; no stridor at rest; and no-to-mild suprasternal, intercostal indrawing (retractions of the skin of the chest wall), or both corresponding to a Westley Croup Score of 0–2. **Moderate croup:** frequent barking cough, easily audible stridor at rest, and suprasternal and sternal wall retraction at rest, but no or little distress or agitation, corresponding to a Westley Croup Score of 3–5. **Severe croup:** frequent barking cough, prominent inspiratory and, occasionally, expiratory stridor, marked sternal wall retractions, decreased air entry on auscultation, and significant distress and agitation, corresponding to a Westley Croup Score of 6–11 (Table1) [5]. For severe croup immediate treatment is with nebulized adrenaline (1:1000 dilution) at a dose of 0.5 mL/kg of body weight to a maximum dose of 5 mL, delivered neat to the nebulizer bow. Dexamethasone and budesonide are effective in relieving the symptoms of croup as early as 30 minutes after treatment [6]. Corticosteroids play a major role in the treatment of pseudocroup due to their vasoconstrictor and anti-inflammatory properties. They reduce vascular permeability and mucosal edema. The main requirements for the "ideal" inhaled corticosteroid are potent and persistent anti-inflammatory effect, rapid penetration into the target tissue, minimal systemic exposure, including low systemic bioavailability, rapid systemic clearance, and minimal cumulative potential. Antibiotics as a prophylaxis against these cases are not recommended. Antitussives and decongestants should not be administered, also there is no clear theoretical reason to use short-acting b2-agonists for treatment of croup [7, 8]. Oxygen must be given via a face mask in moderate to severe croup. The aim of this study was to evaluate the frequency, treatment, and possible complications of croup syndrome in children hospitalized at our institute.

Table 1. Clinical scores for assessing severity of croup

Croup scoring systems
Downes and Raphaely Croup Score Total score ranging from 0-10 points. Five component items make up the score: - inspiratory breath sounds (0=normal, 1-hard with rhonchi, 2-delyed) - stridor (0-normal, 1=inspiratory, 2=inspiratory and expiratory) - cough (0-none, 1=hoarse cry, 2=bark) - retraction/nasal flaring (0=normal, 1=suprasternal/present, 2=suprasternal and intercostal present) - cyanosis (0=none, 1=in room air, 2= in FIO2 0.4) Taussing Croup Score Total score ranging from 0-14 points. Five component items make up the score: - colour (0=normal, 1=dusky, 2=cyanotic in air, 3=cyanotic in 30-40% oxygen) - air entry (0=normal, 1=mildly diminished, 2= moderately diminished) - retractions (0=none, 1=mild, 2=moderate, 3=severe) - level of consciousness (0=normal, 1=restlessness, 2=lethargy [depression]) - stridor (0=none, 1=mild, 2=moderate, 3=severe [or no stridor in the presence of other signs of severe obstruction) Westley Croup Score Total score ranging from 0-17points. Five component items make up the score: - stridor (0=none, 1=with agitation only, 2=at rest) - retractions (0=none, 1=mild, 2=moderate, 3=severe) - cyanosis (0=none, 4=cyanosis with agitation, 5= cyanosis at rest) - level of consciousness (0=normal [including asleep], 5=disorientated) - air entry (0=normal, 1= decreased, 2=markedly decreased)

MATERIALS AND METHODS

Our Institute is the largest of its kind in our country and specializes in pediatric pulmonology. During the last year, 33.763 children were examined at the Institute, out of which 3344 were hospitalized, of which about 500 children were initially placed in the unit for close monitoring and semi-intensive care.

Of all 500 children, 10% were with croup. In our retrospective study we examined 56 pediatric cases with croup syndrome that were hospitalized in our Institute and we analyzed gender and age, the season in which we had the most frequent hospitalizations of children with croup syndrome, as well as treatment and possible complications after completion of croup symptoms. Period of examination was one year.

RESULTS

We analyzed our data with Statistical Package for the Social Sciences (SPSS) 17.0. Mean age at diagnosis of children with croup was 26,5 ±2.6 months - range from 45 days to 8 years (Figure 1). As well as the world statistics we got a larger number of hospitalized boys with croup syndrome, rather than girls. The male: female (M: F) ratio was 2.3:1. The peak season incidence of croup was autumn. As far as the days spent in hospital, they ranged from 1 to 14, with 5 days medium duration of stay.

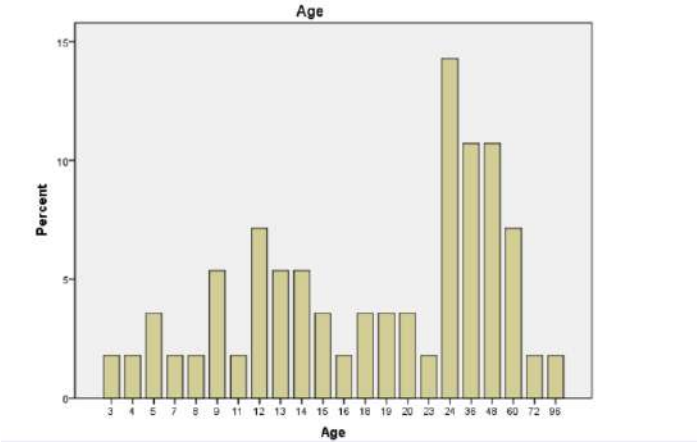

Fig. 1. Age of children hospitalized on ICU.

About the initial treatment all of patients were treated with nebulized adrenaline. Regarding parenteral and inhaled corticosteroids, we received data that 85.7% received parenteral (methylprednisolone), while 87.5% (n= 49) received inhaled corticosteroid, budesonide (Table 2).

Table 2. Percentage of administered intravenous and inhaled corticosteroids

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
I.V.Corticosteroids	48	85,7%	8	14,3%	56	100,0%
InhaledCorticosteroids	49	87,5%	7	12,5%	56	100,0%

But what deviates from world statistics is the high number of antibiotics used during and after hospitalization. As many as 35.7% of the children received i.v. antibiotic and oral antibiotic 48.2%.-total percentage of antibiotics use 83,9% (Figure 2). After the hospital treatment, 50 % of the patients were discharged with oral antibiotics, and 94.6% with inhaled corticosteroids.

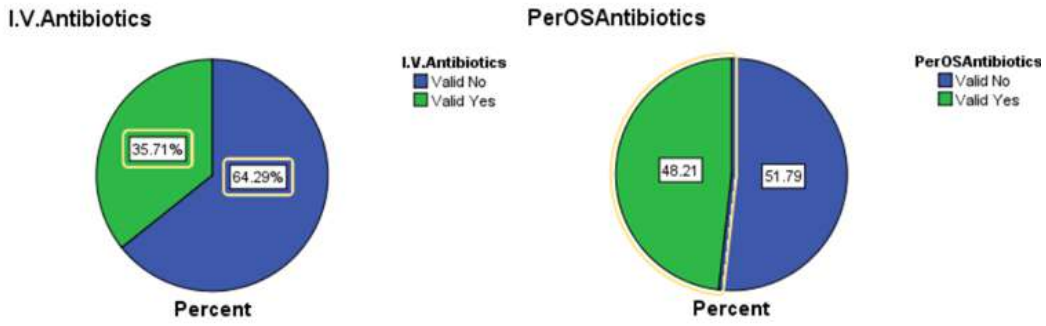

Fig. 1. Percentage of administered I.V. antibiotics and per oral antibiotics.

The most common croup complications were pneumonia and bronchopneumonia (7.1%), bronchitis (3.6%), enterocolitis (1.8%), and tracheobronchitis (3.6%) (Table 3).

Table 3. The five most common comorbidities of croup

Complications

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	/	42	75,0	75,0	75,0
	bronchitis	2	3,6	3,6	78,6
	bronchopneumonia	4	7,1	7,1	85,7
	enterocolitis	1	1,8	1,8	87,5
	pneumonia	4	7,1	7,1	94,6
	tracheobronchitis	2	3,6	3,6	98,2
	tracheomalacia	1	1,8	1,8	100,0
	Total	56	100,0	100,0	

DISCUSSION

Croup syndrome is one of the most common research conditions in the pediatric population, although guidelines for admitting children with this condition and treatment are well known. However, more major studies have been epidemiologically generic except for the period of the croup syndrome due to the geographical location of the countries.

The difference is generally in the treatment of these patients. In this retrospective study of 56 hospitalizations of children with croup in 2019, we analyzed the distributions of age, sex, treatment, and management of patients with croup.

Our results showed that the mean age of patient was 26.5 months, and male dominancy with M: F ratio 2.3:1 that is in accordance with almost all previous reports. One of them was research of Rosychuk et al., (2010) in big Canadian study [9] and Orntoft et al (2013) [10]. According to the months from October to early December in which we had the most of our patients with croup, the pick season is mid to late autumn. The results did differ from children and adolescents with croup and epiglottitis who visited 146 emergency departments in Korea (July with 11.6% of all ED visits, August, March, and April had the next highest incidences with 10.8%, 10.4%, and 10.1%, respectively), Lee et al.,(2015) [11] but are in correlation with the statistics form Croup Hospitalizations in Ontario, Segal et al., (2005) [12]. About the treatment, if we take into consideration that all of the admitted patients were with moderate to severe croup presentation, the initial treatment was with nebulized adrenalin in all of the 56 patients [13]. According to randomized controlled trials (RCTs) or quasi-RCTs involving children with croup evaluated in an emergency department (ED) or admitted to hospital, nebulized adrenalin was associated with improvement of the croup score in 30 min and significantly shorter hospital stay (Kawaguchi et al., 2015) [13]. In 87.5% (n=49) of the patients nebulized corticosteroid was given and in 85.7% parenteral methylprednisolone, which is in correlation with Universal guidelines for the diagnosis and management of croup [14, 15], including those released by the Alberta Medical Association that dictate the use of nebulizing or oral glucocorticoids in all children who receive a diagnosis of croup [12].In spite of the fact that neither of the guidelines recommend giving antibiotic therapy in croup, during and after the hospitalization significant number of our patients have received antibiotics.

Intravenous antibiotics were given in 35.7% of the children oral antibiotic in 48.2%, total percentage of antibiotics use 83,9%. After the hospitalization of the ICU, 50% of the patients were discharged with oral antibiotic. Although the croup is mostly viral infection, most of the patients initially had high inflammatory markers that lead the pediatrician to start with antibiotic course. In a Polish study from 482 patients in 58.1% were given antibiotics (Pejcz et al.2004) [16]. There are a lot of articles and scientific papers that show that giving antibiotics doesn't shorten the days of hospitalization. But if we look back at the comorbidities that are 25%, and if we take into consideration the social and economic status of the country, secondary bacterial infections in children are very common.

Most studies show that the most common form of croup is moderate, 1-8% need hospitalization and only 3% need intubation [7]. In our study, on the contrary, as many as 50% of children needed hospitalization, leading to a conclusion that the admission criteria should be a subject of further reassessment. Administering nebulized adrenalin in the emergency room with subsequent several hour observations may avoid unnecessary hospitalizations. Use of antibiotics for predominantly viral infection remains to be questioned and rationalized.

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CASE REPORT

MOOREN'S ULCER –A CASE REPORT

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ABSTRACT

Introduction: Mooren' s ulcer is a painful, relentless, chronic ulcerative keratitis that starts peripherally and progresses circumferentially and centrally. Mooren's ulcer is a rare corneal ulcer and it is important to be recognized early and treated properly. The different clinical symptoms and local sings and presentation (unilateral or bilateral) of corneal Mooren's ulcer, separate this entity in two groups, benign-limited form and aggressive or progressive form with severe symptoms and morbidity, high tendency for recurrence and increased risk of unsuccessful treatment.

Case presentation: A case of Mooren's ulcer in a female patient 65-year-old is present. She was treated at the University Clinic for eye disease in Skopje after one month of leech extraction of her left eye. The patient came at the Clinic as urgent case with melting syndrome of the peripheral left cornea. Slit lamp examination of the anterior segment confirm the Mooren's ulcer clinical characteristic such as crescent-shaped, peripheral half-circumferential corneal ulcer which start from the limbus with gray infiltrated margin. The sclera around was not involved. The patient complained of pain in her eye and blurred vision. Red eye, foreign body sensation and epiphora were present also. Corneal and conjunctival culture was taken. The lacrimal canal was examined with the straight lacrimal cannula on a 3 ml saline –filled syringe inserted into the lower canaliculus. There was no obstruction in the upper or lower or the common canaliculus. The lacrimal canaliculus was without secretion.

Conclusion: A proper, rigorous and early treatment of the Mooren's ulcer is important for improvement of the local status of this peripherally circumferential melting syndrome. The leech extraction from the patient left eye, a month before, maybe is one of the key factors in the pathogenesis of Mooren's ulcer.

Keywords: Mooren's ulcer, therapy, clinical characteristic, etiology, corneal melting syndrome.

INTRODUCTION

Mooren's ulcer is a painful, relentless, chronic ulcerative keratitis that begins peripherally and progresses circumferentially and centrally [1]. Mooren's first describe this corneal clinical entity in 1867 [1] and that's why this peripheral ulceration was named by him. It is very rare peripheral ulcerative keratitis and its etiology is not fully understood. It is thought that this keratitis is caused by an ischemic necrosis resulting from vasculitis of limbal vessels. It has been shown that the conjunctiva around the ulcer produces enzymes such as collagenase and proteoglycanase which has a certain role in the causation of the Mooren' s ulcer. Trauma, corneal surgery, infection such as parasitic and hepatitis C are mention in the literature that are leading to corneal melting syndrome such as Mooren' s ulcer. The relationship of the systematic disease with the Mooren' s ulcer is poorly understood also [2].

The incidence and severity of the Mooren' s ulcer vary geographically, its rare in the northern hemisphere and common in the Africa (southern and central part), China and India [3,4].

CASE REPORT

A patient 65-year-old woman was treated at the University Clinic for eye disease in Skopje after one month of extraction of leach from her left eye. After extraction, the local antibiotic drops and ointment were prescribed such as ciprofloxacin and chloramphenicol. The symptoms of red eye, foreign body sensations and epiphora were gone after 10 days and the patient returned to the ophthalmologist for the control examination. The far vision acuity was normal. The patient could not read with her dioptric glasses and a prescription of new dioptric lenses for near vision was given to a patient. The ocular pressure was normal on both eyes. After 10 days of the control examination, the patient feels a sensation of foreign body in her left eye which was red and return to the ophthalmologist. The ophthalmologist prescribed the local antibiotics ciprofloxacin drops and corticosteroids drops. After ten days the local symptoms as redness, sensation of the foreign body and epiphora were not improving and the patient started to complain of pain in her left eye. The patient came as urgent case at the Clinic with melting syndrome of the peripheral left cornea. The vision acuity on the right eye was 1,0 without correction and 0,3 with and without correction on the left eye. Slit lamp examination of the anterior segment confirm the Mooren's ulcer clinical characteristic such crescent-shaped, peripheral half-circumferential corneal ulcer which start from the limbus with gray infiltrated margin. The sclera around was not involved. The patient complains of pain in her left eye and blurred vision. Red eye, foreign body sensation and epiphora were present also. Corneal and conjunctival culture was taken. The lacrimal canal was examined sued with the straight lacrimal cannula on a 3 ml saline –filled syringe inserted into the lower canaliculus. There was no obstruction in the upper or lower or the common canaliculus. The lacrimal canaliculus was without secretion. The differential blood count was taken, erythrocyte sedimentation rate, antistreptolyzine and rheumatoid factor (RF) were tested. The result of this investigation were in normal range. The patient was treated with local antibiotics drops such as moxifloxacine (fluoroquinolone drops from the fourth generation) and chloramphenicol ointment. The patients complain after the application of chloramphenicol ointment, such as sensation of foreign body, painful burning and discomfort. As that the ointment was excluded. Also mydriatics drops were prescribed twice a day and local corticosteroids and non-steroid drops. The use of topical corticosteroids was tapered based on the patient's response to the treatment. The system antibiotics therapy such as ceftriaxone injection was given for 7 days. Day by day the reepithelization of the corneal epithelium starts to cover the peripheral ulcer from the limbus and grays margin to the active margin of the ulcer near by the center of the cornea. The neovascularization of the conjunctiva starts to profound the limbal cornea. The healing takes place from the periphery leaving a thin vascularized and opaque cornea. The patient was regularly visited the Clinic for checking on month bases in the beginning, and on tree months after it. After 6 months, patient complain of epiphora and red eye and local antibiotic therapy such as moxifloxacin (fluoroquinolone drops from the fourth generation) combined with the tobramycin were prescribed. Also other eye drops were prescribed such as dexamethasone and mydriatics. The slip lamp examination, confirm the recurrences of the Mooren's ulcer. There was involved active elevated margin of the ulcer near by the center of the cornea. After 24 months of following the patient, there is no recurrence or worsening of the Mooren's ulcer.

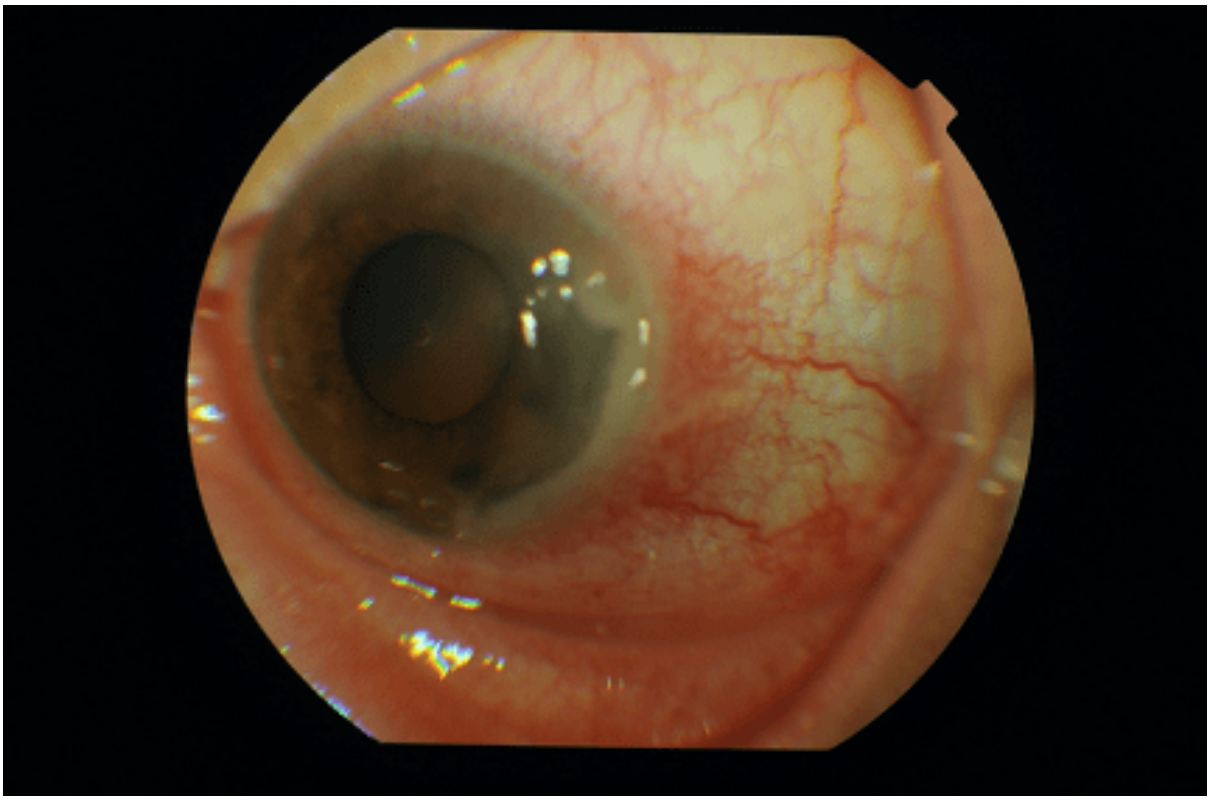

Fig. 1. Mooren's ulcer before the treatment.

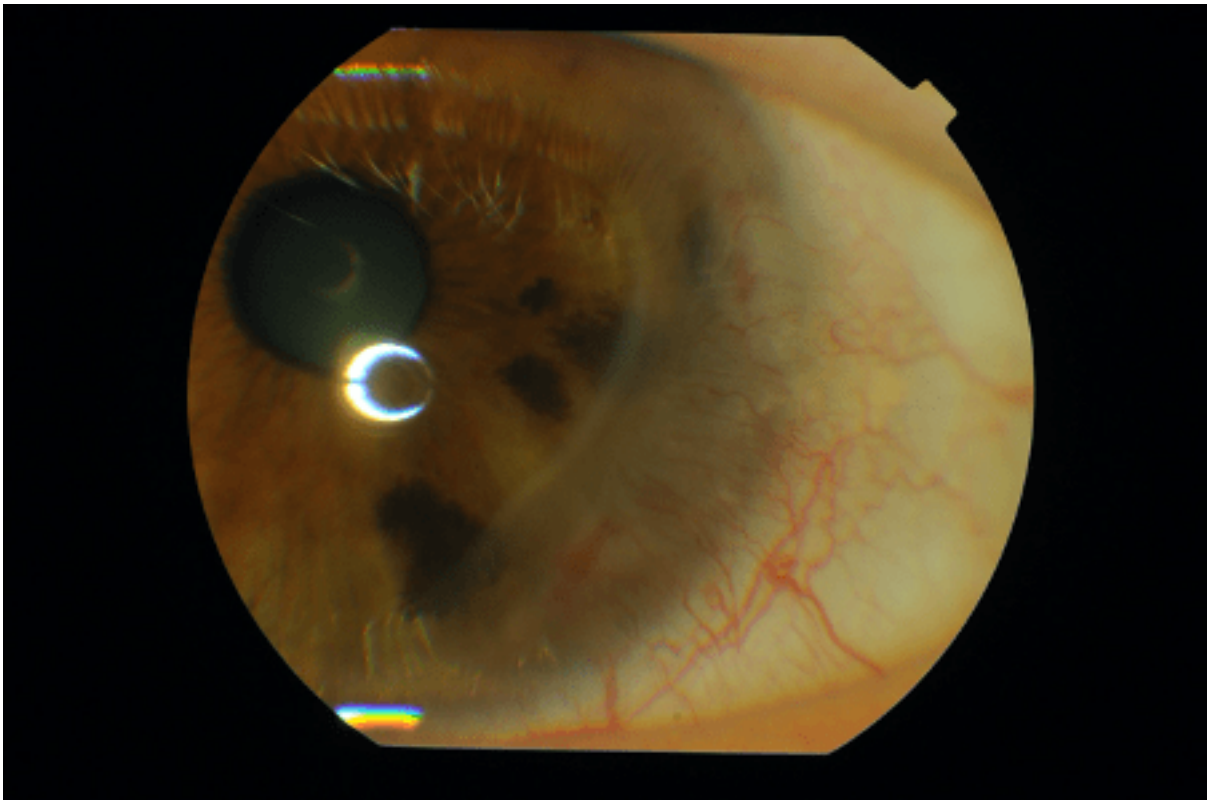

Fig. 2. Mooren's ulcer after one month of the treatment.

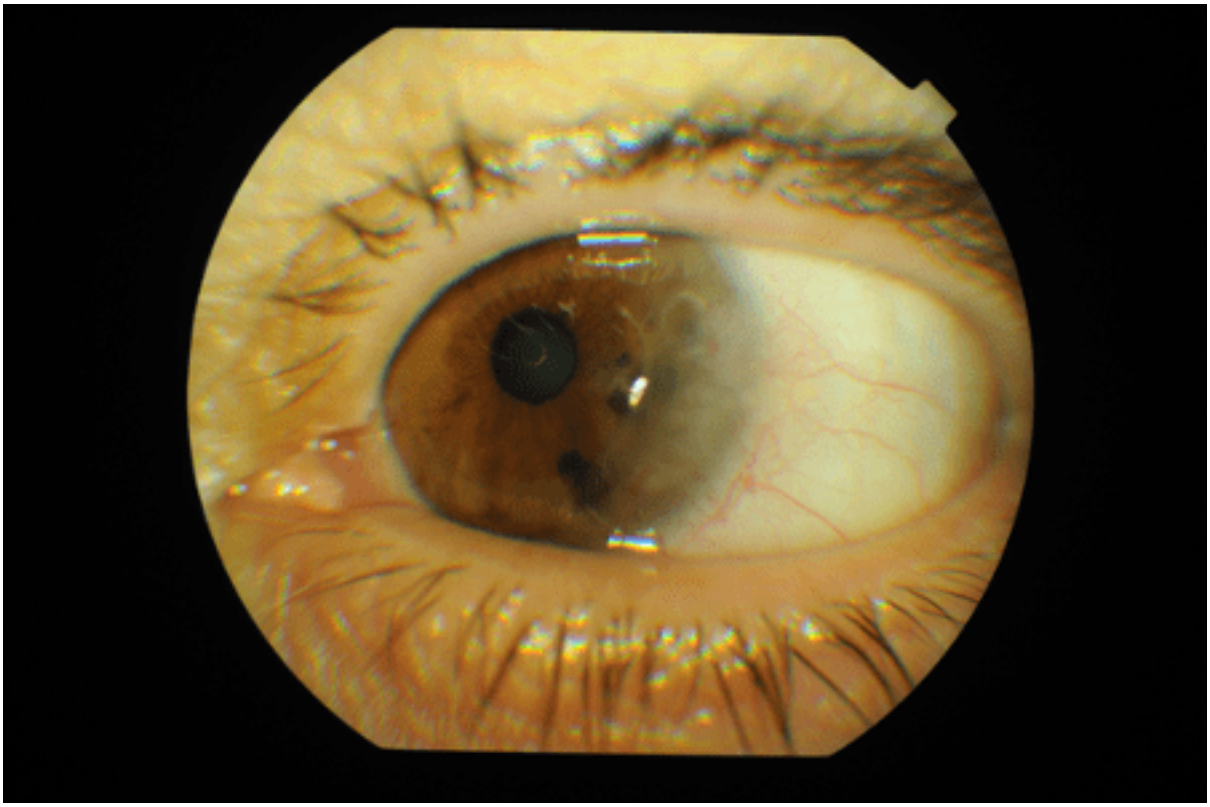

Fig. 3. Mooren's ulcer recurrence after 6 months.

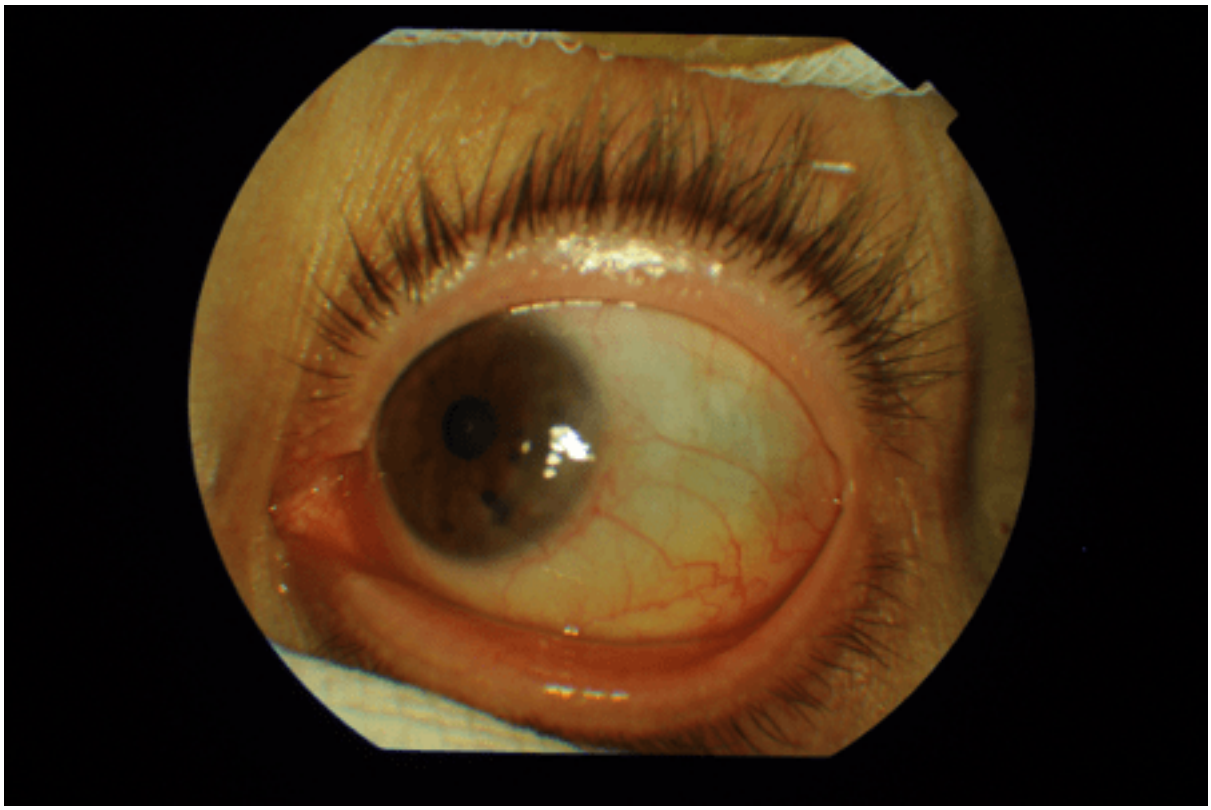

Fig. 4. Status of the cornea after 24 months of the beginning of the Mooren's ulcer treatment.

DISCUSSION

Wood and Kaufman [5] classified this disease in two groups according to the age of onset, clinical characteristic and prognosis of nine cases. The two types of Mooren's ulcer are: benign responsive to therapy which is usually unilateral and mostly affects the elderly and the other a progressive form which is bilateral and typically affects relatively young individuals with relatively more pain and generally a poor response to the therapy. But many ulcers due to difference of course or response to therapy cannot be simply classified in this convenient classification, because of complex underlying pathology. This is underlined by the range of histopathological data obtained in several studies of this rare condition [6].

Recently it has been suggested that the more general term corneal melting syndrome would be more appropriated because the etiology and relationship of Mooren's ulcer to systematic diseases are also poorly understood [6].

Previous studies supported that corneal trauma, surgery and infection were risk factors for Mooren's ulcer [7-9]. There were no signs of bacterial infection in the agar of Petri's cup from the corneal and conjunctival specimen taken from the anterior segment of the eye of the patient involved in our study. But we could not forget that the patient was treated with local antibacterial ciprofloxacin and chloramphenicol and anti-inflammatory corticosteroid drops such as almost 3 weeks before the corneal and conjunctival swab was taken.

Young and Kim reported separately that 48% [10] and 41.7% [3] has a history of ocular surgery, corneal trauma or infection. Zegans and Srinivasan [11] confirmed significant association and Mooren's ulcer formation in his prospective study of 21 patients in India, and 68% of the patients had a history of corneal trauma, surgery and infection. In the same study the authors confirmed a significant association between hookworm infection and Mooren's ulcer formation. In our case report, extraction of leech was done a month before a Mooren's ulcer was diagnosed of the same eye which probably is the cause and trigging factor for the corneal melting syndrome in our patient.

Some authors such as Ye, Chen, Kim and Yao confirmed that Mooren's ulcer is result of an autoimmune process. In this autoimmune process the humoral and cell-mediated components are involved [12,13]. In the sera of patients with the Mooren's ulcer Co-antigen (cornea associated antigen was found [14,15)]. Co-ag might be a protein calgranulin C which is involved in the immune response to parasitic infections and it's also found in the corneal stroma [14,15]. There for, calgranulin C maybe a key factor in the pathogenesis of Mooren' s ulcer.

The recurrence of the Mooren's ulcer in some studies were related with corneal infection and corneal perforation [10]. The recurrence of Mooren's ulcer, still is a big issue in the management of this corneal peripheral ulcer. The prevalence of Mooren's ulcer and the blindness caused by the disease is unknown [3]. The treatment is difficult and includes different options regarding of the type and stage of the Mooren's ulcer. Usually topical therapy with antibiotics and corticosteroids drops is the initial approach. In patients with bilateral ulceration with worse prognosis for the vision acuity and the eye ball, systematic therapy with steroids, cyclosprin and cytotoxic drugs are required. In some cases, resistant to the therapy, the conjunctival excision, parallel to the ulcer may be required and effective. Other surgical interventions such as, keratoepithelioplasty and lamellar keratoplasty is widely used [13,16]

CONCLUSION

A proper rigorous and early treatment of the Mooren's ulcer can improve the local status of this peripherally circumferential melting syndrome. The infection from the leach extraction a month before the diagnosis of the Mooren's ulcer in our patient, maybe is one of the key factors in the pathogenesis of this condition.

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CASE REPORT

A PATIENT WITH ANCYLOSING SPONDYLITIS –BECHTEREV DISEASE AND FRACTURE OF C4, C5 WITH PRIMARILLY QUADRIPLEGIA

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ABSTRACT

The ankylosing spine is usually prone to fracture after minor trauma. Our patient fell on ice in the skiing center Popova Shapka and he immediately felt severe pain in the cervical spine without neurological deficit in the first moments after injury. He was transported rapidly with a solid immobilization of the cervical spine on a special table to the University Clinic for Traumatology in Skopje. When he arrived in Skopje, we detected a complete quadriplegia, and he was hospitalized at the Trauma department. He was admitted in the Intensive care unit where RTG investigation, CT-scan and MRI of the cervical spine were performed. We found a complete disruption on level C4, C5 with a soft tissue compression on spinal canal from the posterior side. We prepared the patient for a posterior approach since in such cases the anterior approach is not possible because of the stiffness of the cervical spine. Also, the compression was posterior, and we used a special elastic cannula for intubation. We performed a decompression and posterior fixation. Synapsis system two levels above and two levels below was used. In such patients with ankylosing spondylitis – Bechterew's disease and fracture of cervical spine we can recommend posterior approach because of the stiffness of the cervical spine and limited chances for performing the anterior approach. We can also recommend decompression combined with a posterior fixation. Anesthesiologists have to use flexible cannula for intubation. Chances for neurological recovery are bigger if decompression is immediately done.

Keywords: Ankylosing spondylitis – Bechterev disease, Fracture of C4,C5, primarily quadriplegia.

INTRODUCTION

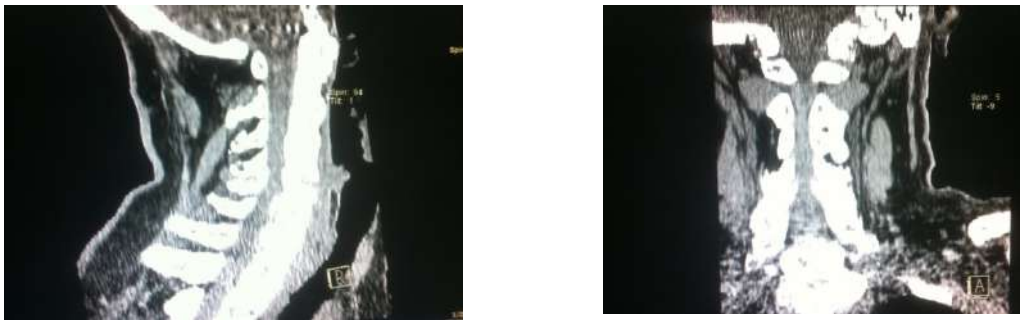
The ankylosing spine is usually prone to fracture after minor trauma. Our patient fell on ice in the skiing center Popova Shapka and he immediately felt severe pain in the cervical spine without neurological deficit in the first moments after injury. He was transported rapidly with a solid immobilization of the cervical spine on a special table to the University Clinic for Traumatology in Skopje. When he arrived in Skopje, we detected a complete quadriplegia, and he was hospitalized at the Trauma department with such a diagnosis.

Several authors have shown that patients with ankylosing spondylitis have a higher fracture risk compared to unaffected individuals. In these patients, fusion of sacroiliac joints and spine occurs due to chronic inflammation followed by a generalized stiffness of the spine. This disease is very rare and has a prevalence of 0.1 -1.4% and usually affects males younger than 30 years, but our patient was 67 years old.

CASE REPORT

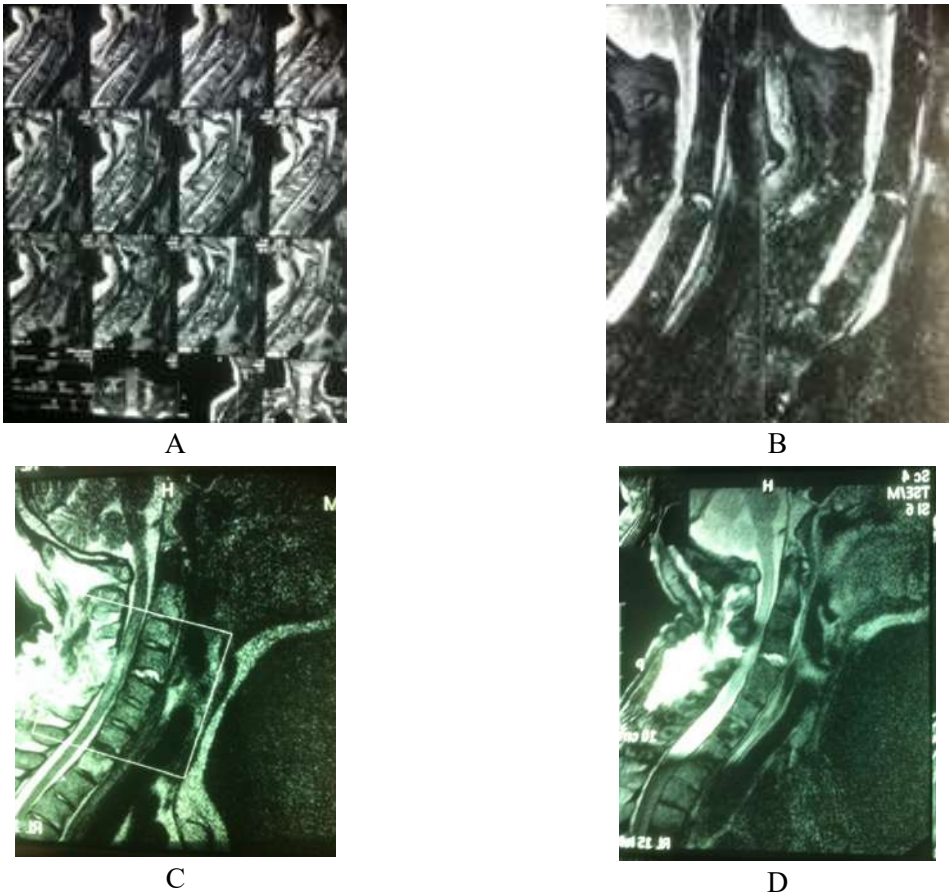
He was admitted at the Intensive care unit where RTG investigation, CT-scan and MRI of the cervical spine were performed. We found a complete disruption on level C4, C5 with a soft tissue compression on spinal canal from the posterior side.

Fractures in ankylosed spine are often unstable due to the ossification of supportive and elastic soft tissues and often they can cause neurologic deficit as a result of dislocation. Neurologic deficit after fracture is a well-known and feared complication in ankylosing spondylitis, therefore these patients should be handled with a great care even and especially when a fracture is suspected. We found a complete motor deficit in both legs and only limited movements in elbows and humeroscapular region. Sensitive sensations below mamilla line were absent. Babinski reflex was positive on both legs. Due to the spinal shock the patient was bradycardic.



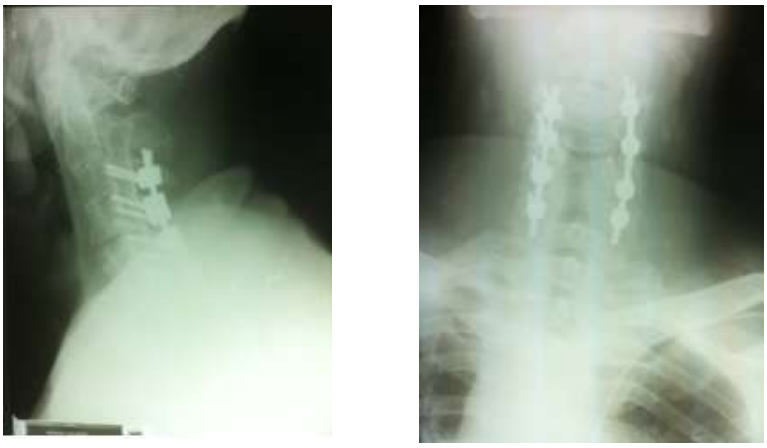
A B

Fig. 1. Preoperative Computed Tomography (CT): A, B.



A B C D

Fig. 2. Preoperative Magnetic Resonance Imaging (MRI): A, B, C, D.



A B

Fig. 3. Postoperative X ray: A, B.

We prepared the patient for a posterior approach since in such cases the anterior approach is not possible because of the stiffness of the cervical spine. Also, the compression was posterior, and we used a special elastic cannula for intubation. We performed a decompression and posterior fixation. After the operation we made a control MRI for visualization of the performed decompression. The patient was given thromboprophylaxis with LMWH according to ACCP. Also, he received corticotherapy according to NASCIS II scale combined with high doses of gastroprotective medications. Postoperatively, the patient was stable with sufficient breathing; there was no need for a respiratory support. After two weeks he was transported to the town where he lived. For one month he had a high temperature of central origin without positive hemoculture.

DISCUSSION

There are uncommon complications of spinal fractures with ankylosing spondylitis described in the literature as aortic dissection, aortic pseudoaneurysm, tracheal rupture and most of them finish lethally, or postoperative wound infection, deep venous thrombosis, pneumonia and respiratory insufficiently. The overall mortality in the posttreatment phase described in the literature is 6.4% [1]. Also, there is a difference between patients surgically treated who have mortality of 4.9% and patients non-surgically treated where mortality is 7.9%. The most frequent cause of death in these patients is pneumonia and respiratory failure. An intrinsic unstable fracture configuration may lead to a primary and secondary neurological deficit [2]. Surgical treatment may be favorable in patients with an ankylosing spine and spinal fracture, as this treatment option may be associated with lower complication and mortality rates and may lead to neurological improvement more frequently [3, 4]. Anesthesiologists have to use flexible cannula for intubation [5]. Chances for neurological recovery are higher if decompression is immediately done [6].

CONCLUSION

Patients with ankylosed spine have an increasing risk of fracture even after minor trauma.

Fractures of the ankylosed spine tend to be unstable, because ossified ligaments and surrounding tissue also fracture. The clinical outcome of patients fracturing their ankylosing spine is worse compared to the general spine trauma population. In patients with ankylosing spondylitis – Bechterew's disease and fracture of the cervical spine we can recommend a posterior approach due to stiffness of the cervical spine and limited chances for performing the anterior approach. We can also recommend decompression combined with a posterior fixation.

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CASE REPORT

ALLERGIC CONTACT DERMATITIS IN A PATIENT WITH STASIS DERMATITIS – A CASE REPORT

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ABSTRACT

Allergic contact dermatitis is a skin condition that occurs because of the immune system's response to an allergen that meets the surface of the skin. Here we present a patient with stasis dermatitis that developed allergic contact dermatitis to various allergens. Patients with stasis dermatitis or any form of cutaneous manifestation of chronic venous insufficiency are at higher risk of developing contact dermatitis with topical medications used to treat dermatitis. We present a case of a 59-year-old male that has used different topical medications to threaten stasis dermatitis and has additionally developed allergic contact dermatitis. He has used topical antiseptics, emollients, corticosteroids, antifungals, and antibiotics. Besides the medicines recommended by the doctor, he also used emollients, as well as herbal remedies of unknown composition. Patients that have a cutaneous manifestation of chronic venous insufficiency are at higher risk of developing contact dermatitis when topical medications are used to repair the lesion. The reason for the increased risk is the frequent occlusive treatments and the chronicity of the disease itself.

Keywords: allergy, contact dermatitis, stasis dermatitis, topical medications.

INTRODUCTION

Allergic contact dermatitis is a skin condition that occurs because of the immune system's response to an allergen that meets the surface of the skin. It is a common inflammatory skin disease characterized by cutaneous eczema and pruritus. Allergic contact dermatitis develops during treatment of chronic venous insufficiency (CVI), including in patients with venous ulceration, in 60% to 80%. The exact mechanisms and why these patients are more likely to develop allergic contact dermatitis with topical medications have not yet been defined. However, there are data in the literature that indicate an increased number of activated cells and an increased production of cytokines and tumor necrotizing factor by monocytes present in stable dermatitis [1].

CASE REPORT

A 59-year-old male was examined at the University Clinic for Dermatology. The patient had persistent swelling, redness, and itching of the lower legs for six weeks, despite the previous diagnosis of chronic venous insufficiency (CVI) and stasis dermatitis more than five years ago.

The medical history also consisted of hypertension, regulated with enalapril for the last two years. For the stasis dermatitis in the lower legs, the patient visited the doctor multiple times and various topical preparations including topical antiseptics, emollients, corticosteroids, antifungals, and antibiotics were applied.

In addition to the medicines recommended by the doctor, the patient also used emollients, as well as herbal remedies of unknown composition. During the last year, the patient noticed a worsening of the condition especially after the application of local remedies, which was the reason for appearing in the hospital.

The dermatological examination showed signs of CVI (edema, telangiectasia and corona phlebctatica, varicose veins, pigmentation, no presence or history of ulceration). In addition, diffuse erythema and edema, affecting the 2/3 circumference of the crural area. Eczematization was more pronounced in pretibial region (Figure 1). Linear excoriations were visible, because of the strong pruritus.

Guided by the previous medical documentation (CVI and DOPPLER findings), the clinical signs of CVI (edema, varicose veins) as well as the clear anamnestic data on the deterioration of dermatological status after application of topical preparations, with a feeling of itching/burning, suggested the possibility that the basic stasis dermatitis was complicated by allergic contact dermatitis.

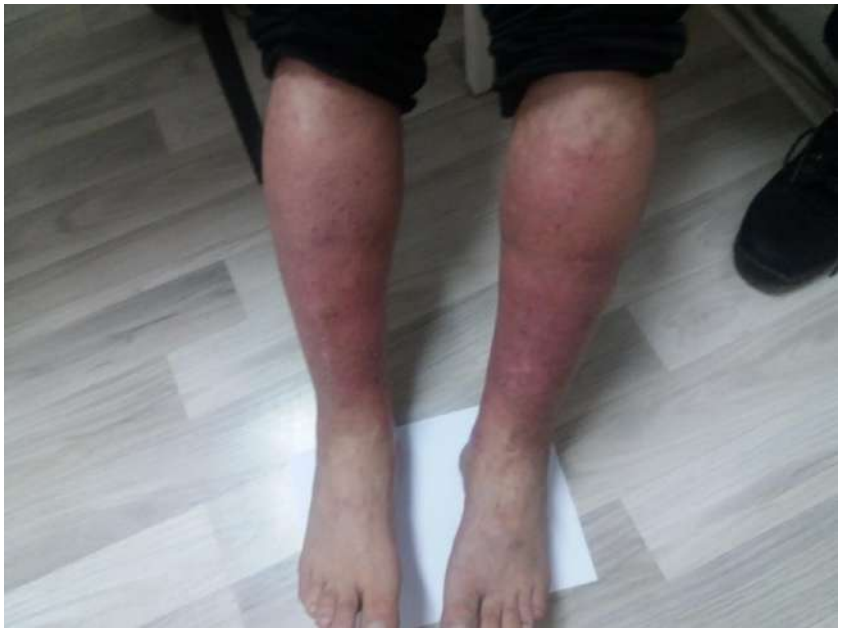

Fig. 1. Skin lesions on the first examination at the Clinic. There are present intensive swelling and redness.

The patient was referred for allergic testing - an Epicutan Patch test with a European basic series (Table 1). The test was performed by marking up to ten chambers with allergens applied on a hypoallergenic paper. The allergens were dissolved in Vaseline or water (Vaselinum album or Aqua destillata) in strictly defined concentrations depending on the active substance. The prepared patches were applied to previously cleansed skin on the patient's back.

Table 1. Basic European series with which the test was performed.

Allergen	Concentration & vehicle	Interpretation
Potassium dichromate	0.5% pet	
p-phenylenediamine (ppd)	1.0% pet	
Thiuram mix	1.0% pet	
Neomycin sulfate	20.0% pet	
Cobalt(II)chloride hexahydrate	1.0% pet	
Caine mix III	10.0% pet	
Nickel(II)sulfate hexahydrate	5.0% pet	
2-Hydroxyethyl methacrylate	2.0% pet	
Colophonium	20.0% pet	++
Paraben mix	16.0% pet	
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0.1% pet	
Lanolin alcohol	30.0% pet	
Mercapto mix	2.0% pet	
Epoxy resin, Bisphenol A	1.0% pet	
Peru balsam	25.0% pet	+++
4-tert-Butylphenolformaldehyde resin (PTBP)	1.0% pet	
2-Mercaptobenzothiazole (MBT)	2.0% pet	
FORMALDEHYDE	2.0% aq	
Fragrance mix I	8.0% pet	+
Sesquiterpene lactone mix	0.1% pet	
QUATERNIUM-15	1.0% pet	
Propolis	10.0% pet	++
Methylisothiazolinonemethylchloroisothiazolinone	0.02% aq	+
Budesonide	0.01% pet	
Tixocortol-21-pivalate	0.1% pet	
METHYLDIBROMO GLUTARONITRILE	0.5% pet	+/ -
Fragrance mix II	14.0% pet	+ /-
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0% pet	
Methylisothiazolinone	0.2% aq	
Textile dye mix	6.6% pe	+

The results were read using the Wilkinson et al method (Table 2). The first reading was after 48h and the second after 72h of the application. The first reading showed a strong positive reaction to Colophonium, an extremely positive reaction to Peru balsam, andoubtful reaction to Fragrance mix I, a strong positive reaction to Propolis, an doubtful reaction to Methyldibromo glutaronitrile. During the second reading, andoubtful reaction to the Fragrance mix II and a weak reaction to textile dye mix was recorded.The patient was instructed to discontinue all topical preparations.

The check up after two weeks showed a significant improvement in dermatological status with withdrawal of the symptoms (Figure 3). The course and outcome of the disease confirmed the suspicion of sensitization of the skin to the topically applied preparations.

Table 2. Interpretation of the Wilkinson et al. scale

(-)	Negative test
(?+)	Doubtful reaction (faint erythema only)
(+)	Weak (non vesicular) reaction (erythema, slight infiltration)
(++)	Strong vesicular or edematous reaction (erythema, infiltrations, vesicules)
(+++)	Extreme (bullous or ulcerative reaction)
IR	Irritant reactions of different types
The results that will be read as false positive and false negative should be counted.	

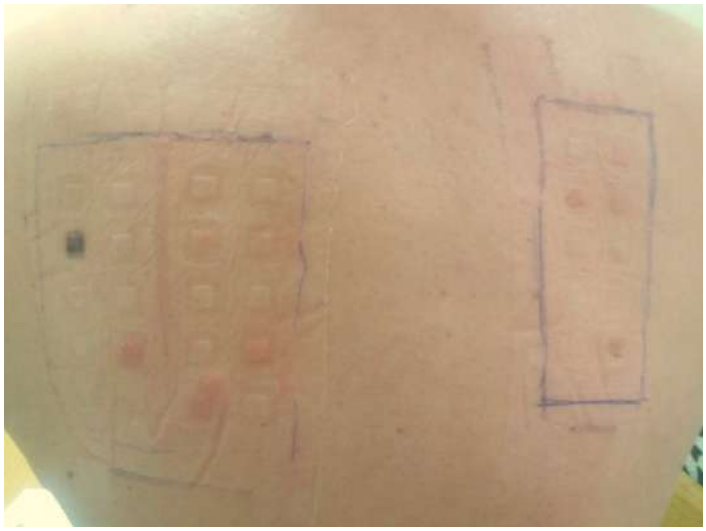

Fig. 2. The first reading of the epicutaneous test.

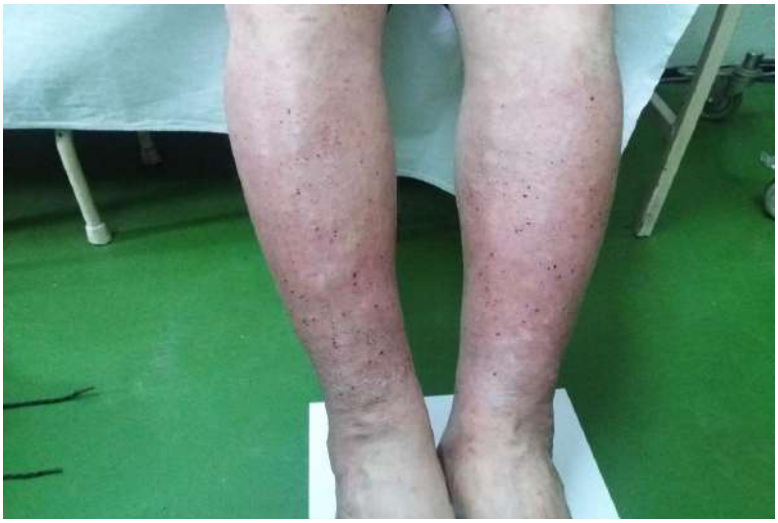

Fig. 3. Clinical picture after applying the given recommendations.

DISCUSSION

Allergic contact dermatitis

There are two forms of contact dermatitis: allergic and irritant. Allergic contact dermatitis is a dermatosis that occurs because of the immune system's response to an allergen that meets the surface of the skin. It is a common inflammatory skin disease characterized by skin eczema and pruritus. The most common causes of allergic contact dermatitis are industrial contact substances that include nickel, chromium, rubber, volatile oils, formaldehyde, turpentine, and others. These may include medications or concomitant medications, including neomycin, benzocaine, antihistamines, lanolin, chloramphenicol, and others. These substances are low molecular weight (<500 Dalton) and are able to cross the corneal layer of the skin. They are not very powerful allergens in themselves, but as they pass through the epidermis, they bind to tissue proteins and form hapten-protein complexes. These complexes trigger an immune system activation and a delayed type of hypersensitivity reaction (Fisher's Contact dermatitis, 6^{th} ed) [1].

-Allergic contact dermatitis is caused by a T-cell-mediated reaction of hypersensitivity. In general, this whole process takes place in two stages. The first phase or induction phase begins with the formation of hapten-protein complexes, which are mentioned above. Such complexes are recognized by antigen presenting skin cells, such as Langerhans and dendritic cells. Antigen presenting cells ingest and process hapten-peptide complexes, forming new hapten-peptide-MHC complexes. The antigen presenting cells then migrate to the lymph nodes, presenting on their surface the hapten-peptide-MHC complexes of the naive T cells. This results in the production of a large number of so-called T cells. Memories T cells that circulate in the blood and are in repeated contact with the same allergen will cause a local skin reaction (Fisher's Contact dermatitis, 6^{th} ed) [2].

The second stage or realization phase is manifested when the skin comes in contact again with the allergen. It occurs 48 to 72 hours after allergen exposure. Memory T cells produce interferon α, interleukins, and other inflammatory mediators that cause macrophages and neutrophils to accumulate in the skin. These cells release enzymes that destroy the allergen, but also destroy the cells in the epidermis and dermis. Due to all these effects occurs inflammation and edema of the skin, which are manifested by redness, itching and edema, and there may be a vesicular eruption at the site of contact [3].

Clinically, acute, chronic, and subacute dermatitis are distinguished. The acute form of allergic contact dermatitis is manifested by erythematous foci accompanied by edema and mild itching. It is possible that small papules appear, rarely, vesicles and bullae are present too, which after eruption create yellowish-brown or brown scales. The chronic form occurs with repeated exposure to the allergen, resulting in dry, thickened skin with a dark red color. Sometimes fissures and lichenification can be present. There are no vesicles and no maceration. The subacute form is a combination of acute and chronic forms [4].

Allergic contact dermatitis typically occurs at the site of contact with the allergen, but it may also occur with an uneven and diffuse distribution. The location of dermatitis can suggest the type of allergen. Thus, if dermatitis occurs on the back of the foot, it may be an allergic reaction due to rubber; if it occurs on the body it can be some kind of textile; if it occurs on the scalp it can be as a result of the shampoo [5]. The predominant symptom is itching, and may be accompanied by burning, itching, or pain.

The diagnosis of allergic contact dermatitis is made on the basis of: [6]

1. The clinical presentation picture. Contact allergic dermatitis may be suspected if the symptoms, described before in the clinical picture are present. Of course, it should be kept in mind that an eruption can occur elsewhere than in the exposed sides. For example, if the allergen is neomycin, it can be applied to other parts of the body and face due to residual remaining amounts on the palms, and after application can give a diffuse form of the disease.

2. History of frequent exposure to a specific allergen. A detailed history is key to detecting all possible allergens that the patient comes in contact with. Everyday habits and the profession are especially important. If a patient gives information about long-term exposure to an allergen that has not previously caused an allergic reaction, two aspects should not be overlooked: sometimes more sensitization is required to manifest the disease, and the second aspect is the health of the patient who changes over time. In addition to age, comorbidities such as stasis dermatitis or ulcus cruris may be present, which play a role in the development of allergic contact dermatitis.

3. Patch tests. Patch tests are very important in diagnosing the disease. They are actually an indicator of the specific allergen that needs to be removed to achieve a therapeutic effect. The test reproduces a small allergic eruption from the suspected allergen. Standardized series are used to perform them, and the results are read after 48, 72, 96 hours and 7 days. If disseminated eruptions are present, Patch tests should be postponed until their withdrawal.

4. Laboratory tests and histopathological verification are not always necessary in the diagnosis of allergic contact dermatitis, but are important for the exclusion of other differential dermatologic conditions

Considering differential diagnose allergic contact dermatitis is difficult to distinguish from irritant contact dermatitis. In general, the dominating symptom of irritant contact dermatitis is burning more than itching and has limited edges table 3. Negative allergic tests and a good effect from topical therapy suggest the diagnosis of irritant contact dermatitis table 1.

Contact allergic dermatitis is usually preceded with a history of contact with known irritants or agents, and with the cessation of the exposure of allergens the eruption is withdrawn. The eruption is with linear configuration, asymmetric and clearly delineated.

Table 3. Characteristics that can differentiate allergic dermatitis from irritant dermatitis

	Irritant Dermatitis	**Allergic Dermatitis**
Location	Usually hands	Usually in exposed skin, not hands
Symptoms	burning, itchiness, pain	Itching is the dominant symptom
Skin manifestations	Dry, cracked skin	Vesicles and bullae
Edges of the lesions	Vaguely delineated edges	Clear angles, lines and borders

Other differential diagnostic conditions to consider include Erysipelas, Lupus erythematosus, Psoriasis, Scabies, fungal infections, and Atopic dermatitis.

Therapy

If left untreated, allergic contact dermatitis can progress from acute to subacute and chronic eczematous dermatitis. The basic rule in the treatment of allergic contact dermatitis is to prevent further contact with the allergen. Topical lipophilic cream with glucocorticosteroids are recommended. In the chronic form, occlusive treatment is performed (Fitzpatrick's Dermatology, Eighth Edition) [7] .

In terms of systemic therapy, corticosteroid therapy is recommended, especially in extensive skin changes where the skin involvement is more than 20%. Antihistamines are given to reduce itching, and antibiotic therapy is given if secondary infection is present [8].

Stasis dermatitis

Chronic venous insufficiency is defined as a condition in which the venous wall and / or venous valves in the legs do not work adequately, resulting in impaired venous flow and making it difficult for the venous blood to return to the heart. This condition results in blood stagnation in the veins, which called venous stasis. This stasis increases the pressure from the deep veins to the peripheral veins and small blood vessels in the skin, which results in changes in the skin itself known as stasis dermatitis [9].

Venous hypertension leads to damage to the vascular endothelium leading to increased leukocyte and platelet attenuation, facilitating their perivascular migration and chronic inflammation, which is also the cause of the dermatological manifestation of the disease. Chronic venous insufficiency manifests itself on the skin in many forms that generally depend on the duration of the disease. In the initial forms there is edema and corona phlebectatica, then it may be spotted bleeding, stable dermatitis, lipodermatosclerosis, atrophie blanche and as the most severe form venous ulcer [10].

Stasis dermatitis is an inflammation of the skin with an exudative nature as a consequence of chronic venous insufficiency. In the acute phase it is manifested by pain, erythema, edema, madidation, and maceration. Stasis dermatitis is treated by treating the primary disease, topical therapy is necessary in order to calm the symptoms. Emollients, topical antibiotics, and corticosteroid therapy may be prescribed. Topical therapy containing rosin, perfumes, balsam of Peru, and other allergens may worsen the clinical picture as a result of allergic contact dermatitis [11].

The connection of allergic contact dermatitis with stasis dermatitis

According to a study by C. Erfurt - Berge, 2017 [12], the percentage of patients with stasis dermatitis who have developed contact allergic dermatitis from topical therapy is 25.9%. A study by Jankićević et al. [7,13] showed that allergic contact dermatitis develops during treatment of chronic venous insufficiency (CVI), including patients with venous ulceration, in a percentage of 60% to 80%. In any case this percentage is high and as a problem is of considerable importance [13-15].

The mechanism by which CVI affects the development of allergic contact dermatitis has not yet been fully elucidated. Histochemical and immunohistochemical analyzes of skin biopsy have shown an increased number of DR + activated cells, promoting HLA class II antigens in patients with stasis dermatitis. Monocytes in stasis dermatitis have been shown to secrete more cytokines, including tumor necrotizing factor alpha (TNFα), interleukin 1ß (IL-1ß), and IL-6. IL-1 and IL-6 are known to be potent activators of the immune system in stimulating Il-2 and T-lymphocyte secretion, proliferation, and differentiation. Il-1 plays a significant role in the presentation of antigen by antigen presenting cells (Langerhans cells) [13].

CONCLUSION

Patients that have a cutaneous manifestation of chronic venous insufficiency are at higher risk of developing contact dermatitis when topical medications are used to repair the lesion. The reason for the increased risk is the frequent occlusive treatments and the chronicity of the disease itself.

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