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CLINICAL UPDATE

GYNECOLOGY // INFECTOLOGY

Paradigm Shift for Endometriosis and the Potential Role of Genetic Testing – Going Beyond the 2022 ESHRE Guidelines for Endometriosis

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ABSTRACT

Endometriosis is a chronic inflammatory gynecological disease affecting 190 million women or 10% of women of reproductive age worldwide. The disease is marked by the presence of endometrial-like tissue outside the uterus, being associated in many cases with chronic pain and infertility. The current recommendations of international professional societies underline the need for laparoscopy, eventually followed by histological verification, as the gold standard for diagnosis. However, many societies recommend the initiation of specific treatment before obtaining a definitive surgical diagnosis. Various national and international societies have released guidelines for endometriosis assessment based on biomarkers; however, none of these recommendations proved to be clinically useful or able to replace diagnostic laparoscopy. In recent years it was demonstrated that oxidative stress, defined as an imbalance between reactive oxygen species and antioxidants that is directly linked with an increased inflammatory response in the peritoneal cavity, may be involved in the pathophysiology of endometriosis. The identification of a genetic predisposition for endometriosis can identify the patients at risk and may help clinicians promptly initiate therapeutic management of their patients in order to ameliorate their prognosis.

Keywords: endometriosis, laparoscopy, biomarkers, oxidative stress

Endometriosis is a chronic inflammatory condition associated with severe pain and subfertility affecting approximately 190 million women and adolescent girls worldwide.[1,2] It is a complex disease of controversial etiology, defined by the presence of endometrial-like tissue outside the uterus. The socioeconomic burden of endometriosis, which affects not only the women with the disease but also their partners, may be similar to Crohn's disease, diabetes, and rheumatoid arthritis, mostly because of the associated infertility and the way it affects the patient's quality of life including work, education, social and intimate life, and general

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wellbeing.[3–6] Furthermore, the average time from symptom onset to diagnosis is currently between 8 to 12 years, which may be explained by the lack of clearly established or accurate noninvasive diagnostic tests or biomarkers.

Treatment options for endometriosis include: 1) surgical treatment, consisting in the surgical removal of endometriotic lesions and adhesions; 2) hormonal treatment, which suppresses endogenous estrogen levels and has proapoptotic and anti-inflammatory effects on endometriotic tissues; 3) the management of chronic pain.[1–6]

The European Society of Human Reproduction and Embryology (ESHRE) has published a series of evidence-based recommendations in their 2022 guideline on the care of women with endometriosis. While the role of these recommendations is clearly established, there is a significant unmet clinical need to improve many aspects related to the diagnosis and treatment of this condition.[6] The aim of this paper is to challenge the current paradigm of laparoscopic identification of endometriotic lesions with histological verification as the gold standard for the diagnosis of endometriosis.

Routinely used in many countries for the diagnosis of endometriosis, laparoscopy is an invasive surgical procedure that requires general anesthesia and is associated with morbidity and even mortality.[7–10] However, given the improvements in the technological caliber and accessibility of imaging modalities for some types of endometriosis on the one hand, and the risks and costs associated with surgery, as well as the difficulty of accessing highly skilled surgeons on the other, there is an urgent need for a revision of this paradigm. Furthermore, it is crucial to develop new noninvasive techniques and improve those that already exist in order to accurately diagnose or rule out endometriosis.[6–8]

Several biomarkers have been proposed for the early, noninvasive diagnosis of endometriosis, but their efficiency has to be demonstrated in clinical studies with adequate outcome measurement and standardized biological sample collection and storage protocols.[6,11,12] So far, the results of the studies assessing the use of these biomarkers in the diagnosis of endometriosis have been disappointing.[6,12,13]

Some of the biomarkers proposed for the diagnosis of endometriosis, such as neuronal marker protein gene product 9.5 (PGP 9.5), vasoactive intestinal polypeptide (VIP), substance P (SP), neuropeptide Y (NPY), or calcitonin gene-related peptide (CGRP), are used to differentiate ovarian endometrioma from other ovarian tumors. However, the available evidence does not support their use for the diagnosis of endometriosis.[6,12–14]

Another proposed biomarker is cancer antigen 125 (CA-125), an inexpensive and widely available tumor marker. A systematic review of 19 prospective and 3 retrospective observational studies involving 3,626 participants with histologically confirmed endometriosis found a specificity of 93% but a sensitivity of only 52% for endometriosis.[6,15] Evidence suggests that CA-125 can be used as a screening marker in symptomatic patients, but its low sensitivity means that a negative result does not rule out endometriosis,[6] and a positive result may cause anxiety for the patient and increase the risk of overtreatment. As a result, studies suggest that CA-125 should not be used routinely for the diagnosis of endometriosis.[6]

Other studies, investigating the clinical usefulness of miRNAs (known to control genes involved in the etiology of endometriosis) as biomarkers of endometriosis, have also yielded mixed results.[6,16,17]

Overall, evidence suggests that currently there are no biological markers that can reliably aid the diagnosis of endometriosis. Therefore, the authors of the 2022 ESHRE guideline concluded that "clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis."[6] This makes genetic testing linked to the pathogenic process of endometriosis an intriguing area of study.[18,19]

Recent studies have focused on other factors that may contribute to the development of endometriotic lesions such as familiar propensity and genetic predisposition. The pathophysiology of endometriosis may involve oxidative stress, an imbalance between reactive oxygen species and antioxidants that results in a general inflammatory response in the peritoneal cavity.[19] Reactive oxygen species are intermediaries produced by the normal oxygen metabolism and are inflammatory mediators known to modulate cell proliferation and to have deleterious effects.[19]

One of our previous studies sought to determine whether there was a relationship between endometriosis-related infertility and four genetic variants of antioxidant enzymes involved in oxidative stress.[18] In this case-control study, the first of this kind in Eastern European women, we investigated the genetic polymorphism of four genes and selected those that encode antioxidant enzymes involved in oxidative stress: glutathione peroxidase 1, GPX1 198Pro > Leu, catalase CAT-262C > T, glutathione S-transferase M1, and T1 null genotype. We investigated the association between these polymorphisms and endometriosis-related infertility in 103 patients with endometriosis-associated infertility and a control group of 102 post-partum women. The variant genotypes were significantly more frequent in the endometriosis group for the CAT-262C > T polymorphism, and the CT and TT genotypes were also significantly more frequent compared in the endometriosis group in respect

to the GPX1 198Pro > Leu. The null genotype of GSTM1 was also detected with a significantly higher frequency in the endometriosis group. However, there were no significant differences between the two groups in respect to the frequency of GSTT1. These results suggested that GPX1 198Pro > Leu, CAT-262C > T, and GSTM1 polymorphisms may predispose patients to develop endometriosis, the association between the GSTM1-GSTT1 null genotype may play a significant role in endometriosis-associated infertility, and the GSTT1 null genotype does not influence the disease.[18] These results are in accordance with two meta-analyses that also concluded that the association of both null genotypes for GSTT1-GSTM1 may be related to endometriosis.[20,21] Given that ethnicity and environmental factors play a significant role in the development endometriosis, some of our findings that are in contrast with data from the literature may be explained by demographic variances.[18]

Therefore, the question arises: is it time to stop using microscopic confirmation of endometriotic lesions as the gold standard for diagnosing endometriosis? Looking at the published results on biomarkers it is hard to declare that this approach is obsolete. For the early diagnosis of this condition, a panel of genetic or laboratory markers is required, especially in the case of young patients who intend to become pregnant in the future. Besides the conventional treatment methods, the management of endometriosis should include strategies that involve the community and ensure a higher quality of life for these patients. These strategies should focus on the establishment of readily available integrated services that increase the standard of care for women with endometriosis, beginning from adolescence.

Over the years, laparoscopy has become the gold standard method for the diagnosis of endometriosis. The preferred method to replace laparoscopy would have to be noninvasive, dependable, and affordable, with good sensitivity and specificity. Large-scale international, multicenter investigations with independent validation using cutting-edge technological platforms, thorough standardized phenotyping, and sufficient financing are urgently needed to move away from the reliance on invasive diagnostic methods like laparoscopy under general anesthesia.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

NEUROSURGERY // PATHOLOGY

Experience in the Morphological Study of Dorsolumbar Spine Deformities in Women over 50 Years

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ABSTRACT

Introduction: Osteoporosis is characterized by a reduction in bone mineral density. Among the factors that can contribute to the onset of osteoporosis we can enumerate alcohol consumption, smoking, glucocorticoid therapy, or the presence of diabetes mellitus. The incidence of osteoporosis increases with age. **Materials and Methods:** A total of 183 women over the age of 50, with a mean age of 67.9 ± 7.74 years, were studied to visualize spinal column alterations. From this cohort, 103 patients underwent bone mineral density testing using dual-energy X-ray absorptiometry (DXA) and dorsolumbar radiography, while 80 patients did not undergo DXA testing. Assessment of the degree of vertebral involvement was performed using the Genant semiquantitative method. **Results:** The highest percentage of vertebral fractures was observed in patients aged >70 years (100%). Within the studied cohort, 28% of patients displayed multiple vertebral fractures associated with age ($p = 0.01$). The most common site for vertebral involvement was the dorsolumbar region (D11–L2) across all age groups ($p = 0.35$). No statistically significant correlation ($p = 0.22$) was identified between DXA values and the presence of vertebral fractures, despite a trend of increased incidence of fractures as the T-score decreased. **Conclusion:** Within the cohort, vertebral fractures were identified both in women with normal values of bone mineral density and in those with osteoporosis. Furthermore, the severity of these vertebral fractures did not correlate with bone mineral density values, highlighting the necessity of using both osteodensitometry and spinal radiographs for diagnosis.

Keywords: osteoporosis, osteodensitometry, dorsolumbar spine

INTRODUCTION

Osteoporosis is a pathological condition that predominantly affects the osseous skeleton, by altering both the microarchitecture and macroarchitecture of the bone. It is characterized by a reduction in bone integrity associated with decreased bone strength, resulting in a porous appearance.[1–4] Osteoporosis is defined as a decrease in bone mineral density (BMD), commonly expressed using the T-score or Z-score, both measured in standard deviations (SD).[1-3,5] Osteo-

porosis is considered a silent disease, often asymptomatic until it becomes the cause of fragility fractures.[2,3,6]

The etiology of osteoporosis is characterized by an imbalance in the bone remodeling process during adult life (bone turnover), with an increase in bone resorption and a decrease in bone formation. Moreover, this process leads to a significant loss of bone trabeculae, with notable differences in the bone microstructure of a patient with osteoporosis compared to a healthy individual. The quality of bone tissue is measured by BMD, which peaks around the age of 30. In women, estrogen helps keep BMD in the normal range, as it maintains a balance in the bone remodeling process. In the extremes of age, BMD is diminished, such that a child exhibits a risk similar to that of their grandmother in developing fractures.[1,7] Among the risk factors, we can enumerate diet, alcohol, smoking, glucocorticoid treatment, and diabetes mellitus.[1,2,6,8]

According to the criteria established by the World Health Organization, in 2010, among the entirety of the European population, approximately 22 million women and 5.5 million men were diagnosed with osteoporosis.[8,9] Advancing age increases the prevalence of osteoporosis.[3]

The diagnosis of osteoporosis and its complications, usually fragility fractures, encompasses several investigations: radiographs of the dorsolumbar vertebral column, hip, or forearm, BMD measurement using dual-energy X-ray absorptiometry (DXA), and histomorphometry.[1,6,8,10,11]

Fragility fractures can occur at any level of the osseous skeleton, but they are particularly prone to appear in the vertebral column, femoral neck, and radius (Colles fracture). In the absence of clinical signs, vertebral deformities, including morphological changes in case of fractures caused by low-intensity trauma, can be more easily observed in lateral incidence.[6,12] Based on the intensity of the injury mechanism, osteoporotic vertebral fractures are classified into three distinct categories: fractures due to minor trauma, in which the patients do not recall the triggering factor of the fracture; fractures due to moderate trauma, caused by forces such as supporting one's own body weight, including during upright posture; and fractures due to high-intensity trauma, which might have occurred even in a healthy bone, but in the osteoporotic bone, it leads to vertebral deformation.[3,6,13–16]

In the case of postmenopausal women, the diagnosis is more complex, necessitating the consideration of the following aspects: a BMD expressed through a T-score below −2.5 SD measured at the lumbar spine or femoral neck; history of vertebral or hip fracture regardless of the value of BMD or other risk factors; a T-score between −1.0 SD and −2.5 SD associated with any of the following: history of fracture localized at the proximal humerus, pelvis, or distal forearm.[1–3,7,8,17–19]

MATERIALS AND METHODS

We analyzed a cohort comprising 183 female patients over the age of 50, with a mean age of 67.9 ± 7.74 years, to visualize spinal column alterations. All patients underwent spinal radiographic examination in two projections (anteroposterior and lateral). From this cohort, 103 patients underwent BMD measurements (using DXA), and a subset of 80 radiographs were analyzed without DXA assessment. The spinal radiographs were performed at the Radiology Department of Dora Medicals medical center in Târgu Mureș using the Siemens Multix Select DX X-ray machine, and osteodensitometry was performed using a GE Lunar Prodigy densitometer.

We identified structural and morphological alterations of vertebral bodies. Vertebral fractures were graded using the semiquantitative Genant grading scheme.[6,20] The interpretation of osteodensitometry results was made based on the following criteria: T-score between 0 and −1 SD – normal values; T-score between −1 and −2.5 SD – osteopenia; T-score below −2.5 SD – osteoporosis.[8]

For statistical analysis we used GraphPad InStat 3 software, version 3.06 (GraphPad Software Inc., San Diego, USA). A significant association was taken into consideration at a p value of $< .05$, with a 95% confidence interval.

Ethics

This study was approved by the ethics committee of "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania (no. 2330/17/05/2023). Written informed consent has been obtained from all participants regarding the publication of this study.

RESULTS

Prevalence of vertebral fractures

The presence of vertebral fractures was identified in 21.8% of cases (40 out of 183) (Figure 1). Among the 80 patients who underwent only spinal radiography, 16.25% (13 out of 80) displayed fractures, while out of the 103 patients who underwent both investigations, 26.21% (27 out of 103) displayed vertebral fractures. No statistically significant association was observed between osteodensitometry and the presence of fractures ($p = 0.85$).

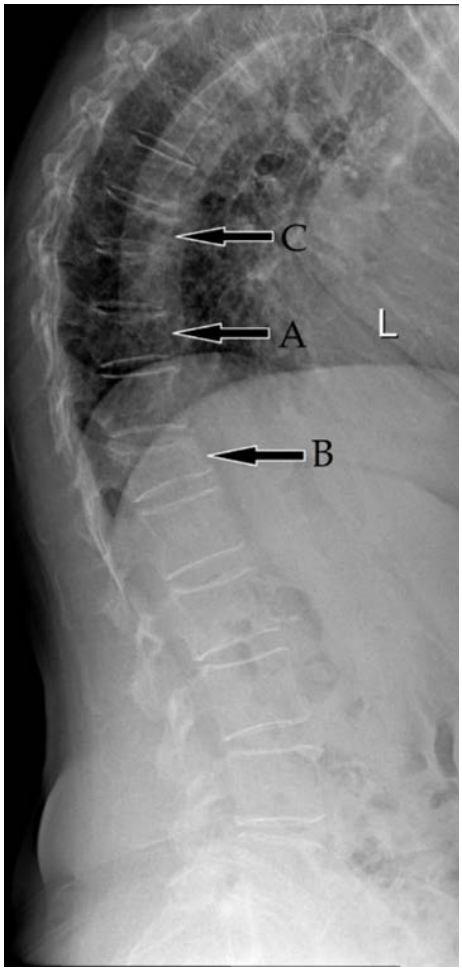

FIGURE 1. **A** – Grade 1 vertebral fracture; **B** – Grade 2 vertebral fracture; **C** – Grade 3 vertebral fracture

Based on the results obtained in the two patient groups (with and without DXA), we observed that there was no statistically significant correlation between the severity grade of vertebral fractures and these two patient categories (p = 0.16). Furthermore, from the total number of cases with vertebral fracture, approximately 52% were from the DXA group and 48% from the non-DXA group. Of the patients with grade 1 vertebral fracture, 60% underwent DXA. Grade 2 vertebral fractures were more frequently encountered among those who underwent bone densitometry, in approximately 80% of cases, while grade 3 fractures had a frequency similar to grade 1 fractures. There was no statistically significant association between bone densitometry and the severity grade of vertebral fractures (p = 0.16).

Severity of vertebral fractures

Analyzing the 50–59 age group, the absence of vertebral fractures was observed in 22% of cases. Of these patients, 41% were diagnosed with grade 1 vertebral compression, 30% displayed grade 2 fractures, and 7% exhibited vertebral fractures corresponding to grade 3. Among patients within the 60–69 age group, 9% exhibited no vertebral involvement, 26% had grade 1 vertebral fractures, 55% had grade 2 vertebral involvement, and only 10% showed grade 3 fractures. In the 70–79 age group there were no patients without vertebral involvement (0%), 13% exhibiting grade 1 vertebral fractures, 66% grade 2 vertebral fractures, and 21% vertebral deformities corresponding to grade 3. From

TABLE 1. Correlation between the severity of vertebral fractures, age, fracture site, and DXA

	Severity of vertebral fractures				p value
	Absent	Grade 1	Grade 2	Grade 3	
Age group (years)					
50–59	32	3	0	2	0.0048
60–69	58	8	2	1	
70–79	43	17	9	6	
80–89	9	3	3	2	
Fracture site					
D8		0	0	1	0.19
D9		1	0	0	
D10		1	0	0	
D11		3	3	4	
D12		13	6	0	
L1		10	2	4	
L2		3	3	4	
L3		2	1	2	
L4		0	1	0	
DXA total	75	20	13	9	0.75
Normal	18	3	3	3	
Osteopenia	38	9	4	3	
Osteoporosis	19	8	4	2	
Non-DXA total	67	13	3	6	0.16

TABLE 2. Correlation between the number of fractures, age, and DXA

	Number of fractures				p value
	Absent	Grade 1	Grade 2	Grade 3	
Age group (years)					
50–59	32	5	0	0	0.01
60–69	58	7	0	2	
70–79	43	10	9	3	
80–89	9	3	1	1	
DXA total	75	17	6	4	0.0658
Normal	18	4	1	1	
Osteopenia	38	3	5	1	
Osteoporosis	19	9	0	2	
Non-DXA total	67	8	3	2	0.43

patients over the age of 80, 19% did not have vertebral fractures, 9% had grade 1 vertebral fractures, 53% were diagnosed with vertebral involvement corresponding to grade 2, and 19% presented vertebral fractures corresponding to grade 3 (Table 1). A statistically significant correlation was observed between the severity grade of fractures and advanced age ($p = 0.0048$).

Number of injured vertebrae

Analyzing both groups, we observed a statistically significant association between the number of fractures and age ($p = 0.01$) (Table 2).

Investigating the relationship between the severity grade of vertebral fractures and the age of patients in the non-DXA group, we found no statistically significant correlation ($p = 0.09$). This indicates that with age, a decrease in the number of cases where patients do not exhibit any vertebral fractures can be observed, and fractures become more frequent. Among patients in the 50–59 age group, 28% did not have any vertebral involvement, 39% had grade 1 vertebral fractures, 27% of vertebral fractures were classified as grade 2, and 6% of patients had grade 3 vertebral fractures. In the 60–69 age group, 9% of cases had no vertebral involvement and grade 3 vertebral fractures, 27% of cases were classified as grade 1 fractures, and 55% of cases had grade 2 vertebral fractures. In the 70–79 age group, 67% of patients had grade 2 vertebral fractures, and 33% had grade 3 fractures.

Analyzing the DXA group, we observed differences in patient involvement concerning age categories, as per the results ($p = 0.22$). In the 50–59 age group, 18% of patients did not have any vertebral involvement, 42% had grade 1 fractures, 32% had grade 2 fractures, and 8% had grade 3 fractures. In the 60–69 age group, 10% of patients did not have any vertebral involvement, 25% had grade 1 fractures, 55% had grade 2 vertebral fractures, and 10% had grade 3 fractures. In the 70–79 age group, there were no patients without any vertebral involvement, 19% were diagnosed with grade 1 fractures, 62% had grade 2 fractures, and 19% had grade 3 vertebral fractures. In the 80–89 age group, 25% of patients did not have vertebral involvement, 13% had grade 1 fractures, 50% had grade 2 vertebral fractures, and 12% had grade 3 fractures.

Sites of vertebral fractures

In the non-DXA group (Figure 2), we observed a statistically significant correlation ($p = 0.01$) between age and the location of the most frequently affected vertebral level, the dorsolumbar junction. In the 50–59 age group, a single vertebral site at D9 was affected. In the 60–69 age group, the dorsolumbar junction was predominantly affected, with a single vertebral involvement at D11, three cases of vertebral involvement at D12, and a fracture at L1. In the 70–79 age group, the same dorsolumbar junction was predominantly affected, with three cases of affected vertebrae at D11, four vertebral fractures at D12, and three affected vertebrae at L1. An additional case of vertebral involvement was identified at the L2 vertebral site and two cases at L3. In the 80–89 age group, we identified one vertebral involvement at D11, L2, and L3, respectively. Among patients in the 60–69 age group, D11, D12, and L1 were predominantly affected, while in the 70–79 age group, D11, D12, L1, L2, and L3 were the most frequently fractured.

In the DXA group (Figure 3), D12, L1, and L2 were affected across all age groups. D8, D9, and L4 fractures were identified only in the 70–79 age group. D11 involvement was identified in 80% of cases in the 70–79 age group and

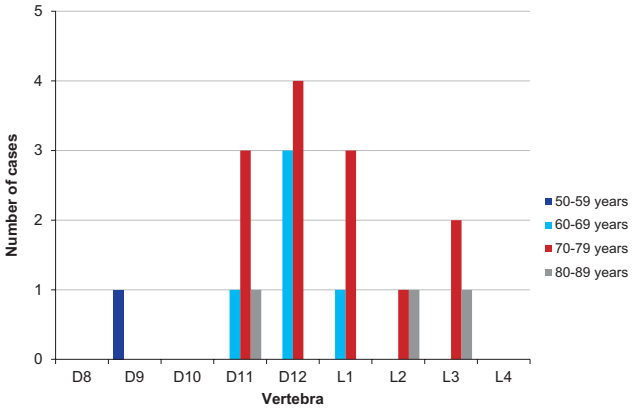

FIGURE 2. Fracture sites by age in the non-DXA group

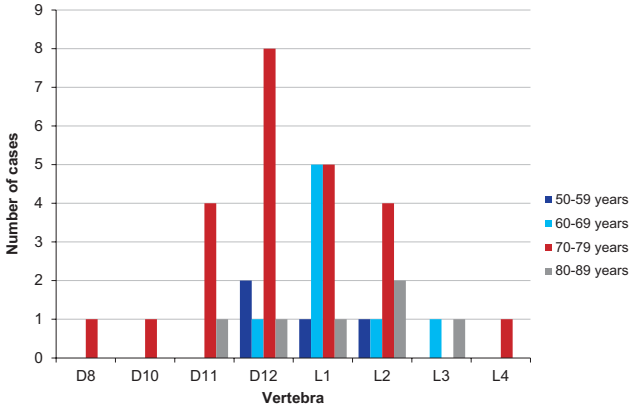

FIGURE 3. Fracture sites by age in the DXA group

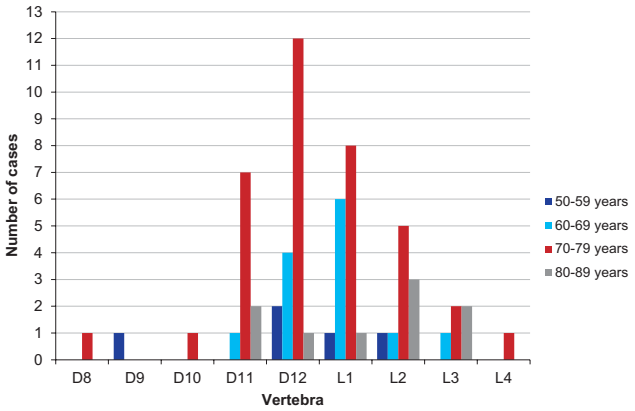

FIGURE 4. Fracture sites by age in all patients

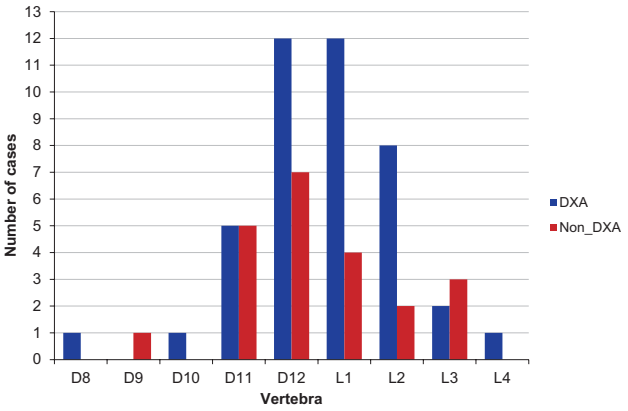

FIGURE 5. Comparison of fracture sites between the DXA and Non-DXA groups

20% of cases in the 80–89 age group. Vertebral site D12 was involved in 15% of cases in the 50–59 age group, 10% of cases in the 60–69 age group, 67% of cases in the 70–79 age group, and 8% of cases in the 80–89 age group. Vertebral site L1 was involved in 8% of cases in the 50–59 age group, 42% of cases in the 60–69 age group, 42% of cases in the 70–79 age group, and 8% of cases in the 80–89 age group. Morphological changes at the L2 vertebral site were identified in 12% of patients in the 50–59 age group, 13% in the 60–69 age group, 50% in the 70–79 age group, and 25% of patients in the 80–89 age group. Vertebral site L3 was equally affected (50%) in the 60–69 and 80–89 age groups. We found no statistically significant correlation in the DXA group between fracture sites and age ($p = 0.81$).

Analyzing all 183 patients included in the study (Figure 4), similarly to the DXA group, the dorsolumbar junction was affected in all age groups; however, there was no statistically significant association between fracture sites and age ($p = 0.35$).

The most common fracture site was the dorsolumbar junction, with significantly more fractures at the D12–L2 level in the DXA group. We found no statistically significant association between the DXA and non-DXA groups regarding the site of vertebral fractures ($p = 0.47$) (Figure 5).

Interpretation of bone densitometry values

From the 103 patients who underwent both spinal radiography and bone densitometry, patients diagnosed with osteoporosis represented 31.06% of the total of cases that underwent bone densitometry, those with osteopenia represented 45.63%, and those with normal values accounted for 23.30%. The age of the patients was significantly correlated with bone densitometry values ($p = 0.05$). The distribution of bone densitometry values is represented in Figure 6. From the patients in the 50–59 age group, 41% had bone densitometry values within normal limits, 41% had values indicative of osteopenia, and 18% had values indicative of osteoporosis. In the 60–69 age group, 29% of patients had normal values, 33% had bone densitometry values indicative of osteopenia, and 38% had osteoporosis. In the 70–79 age group of, 10% of cases had normal bone densitometry values, 62% had values indicative of osteopenia, and 28% had values indicative of osteoporosis. In the 80–89 age group, 25% had normal values, 25% had values indicative of osteopenia, and 50% had values indicative of osteoporosis. Therefore, it can be stated that the incidence of osteoporosis increases with age, ranging from 18% between 50 and 59 years to 50% between 80 and 89 years. Similarly, the incidence of normal values decreases from 41% between 50 and 59 years to 25% between 80 and 89 years.

We found bone densitometry values to be correlated with fragility fractures, as 73.78% of patients in the DXA group did not exhibit deformities, and only 26.21% had vertebral

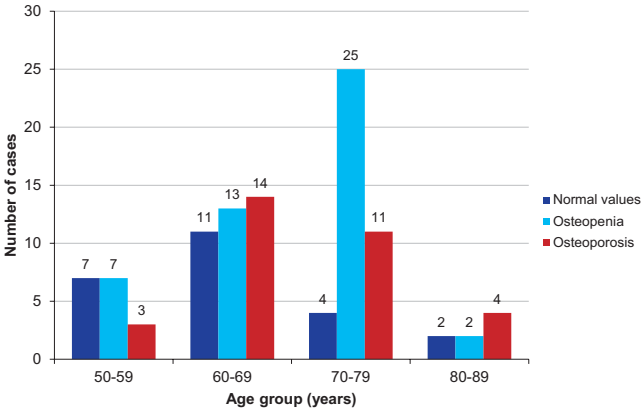

FIGURE 6. Bone densitometry results

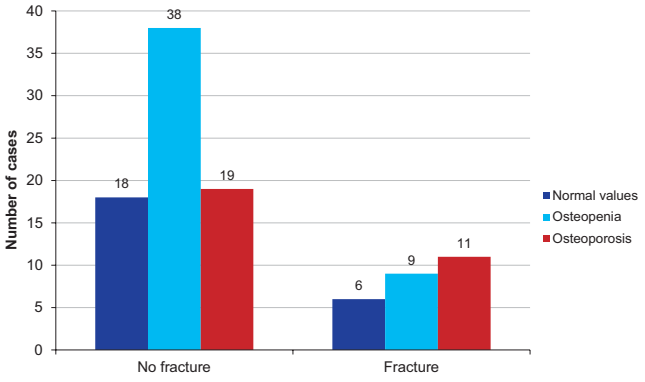

FIGURE 7. Presence of vertebral fractures based on bone densitometry values

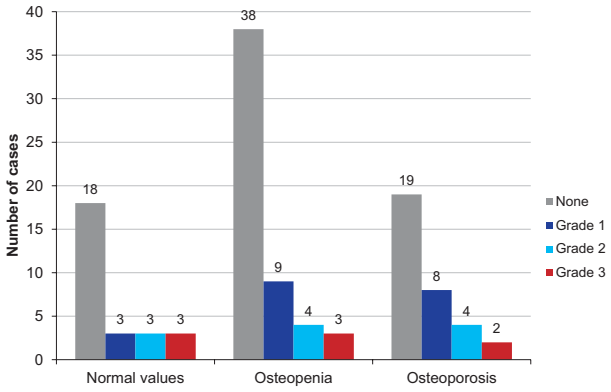

FIGURE 8. Correlation between the number of fractured vertebrae and DXA

fractures. Among patients with vertebral fractures, 25.92% had normal bone densitometry values, 33.33% had values indicative of osteopenia, and 40.74% had values indicative of osteoporosis. Among those without vertebral fractures, 23.68% had normal values, 51.31% had values indicative of osteopenia, and 25% had values indicative of osteoporosis (Figure 7). Although the number of cases with fracture increased with a decreasing T-score, we found no statistically significant correlation between DXA values and the presence of vertebral fractures ($p = 0.22$).

Figure 8 suggests that there is an almost statistically significant correlation ($p = 0.0658$) between osteoporosis and the number of vertebral fractures, indicating that as the T-score value decreases, the number of affected vertebrae increases.

In the analyzed cohort, 75% of patients did not display any vertebral involvement and their bone densitometry values were normal, 17% of patients had a single affected vertebra, 4% had two affected vertebrae, and 4% of patients had three or more affected vertebrae. In the case of patients exhibiting values indicative of osteopenia, 81% had no vertebral involvement. From these patients, 5% had one affected vertebra, 11% had two affected vertebrae, and 2% had three or more affected vertebrae. Regarding patients diagnosed with osteoporosis, 62% had no vertebral involvement, in 31% a single vertebra was affected, and 7% had three or more affected vertebrae.

Regarding the relationship between bone densitometry values and the most frequent fracture sites (Figure 9), we observed that vertebral fractures were predominantly present in the D11–L3 segment in patients with normal or osteopenic bone densitometry values. In cases of osteoporosis, along with these vertebrae, distant vertebrae from the dorsolumbar junction, such as D8–D10 or L4 were also affected.

The statistical analysis showed that 100% of the time when the D8, D10, and L4 vertebrae were affected, osteodensitometry values were specific to osteoporosis. Of the patients with D11 involvement, 20% had normal bone density values, 60% had osteopenia, and 40% had osteoporosis. Of the patients with D12 involvement, 25% had normal osteodensitometry values, 40% had osteopenia, and 35% were diagnosed with osteoporosis. Of the patients with L1 vertebral involvement, 18% had normal osteodensitometry values, 32% had osteopenia, and 50% had osteoporosis. Of the patients with L2 involvement, 38% had normal bone density values, 37% had osteopenia, and 25% had osteoporosis. When the L3 vertebra was affected, 50% of patients had normal osteodensitometry values and 50% had osteoporosis. However, we found no statistically significant correlation between bone densitometry values and fracture sites ($p = 0.81$).

We analyzed the correlation between the severity of vertebral fractures and osteodensitometry values (Table 1). Of the patients who did not have vertebral fractures, 25% had normal bone density values, 50% had values in-

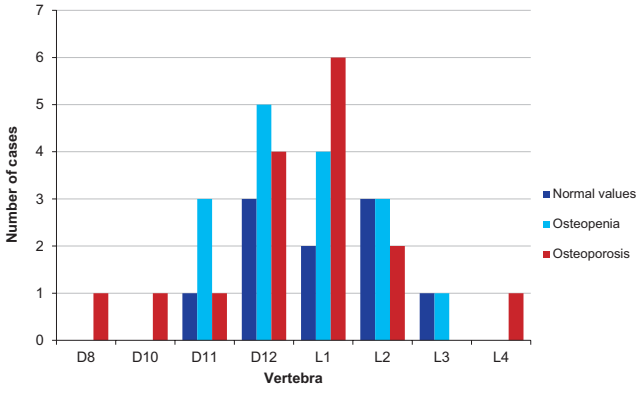

FIGURE 9. Correlation between DXA and fracture sites

TABLE 3. Bone densitometry data in our study and in the literature

DXA	Yang *et al.*[21]	Alshaali *et al.*[22]	Cai *et al.*[23]	Present study
Osteoporosis	31.50%	48.30%	51.19%	31.06%
Osteopenia	42%	40.90%	40.20%	45.63%
Normal values	26.50%	10.80%	8.56%	23.30%

TABLE 4. The number of fractured vertebrae in comparison with our study

No. of fractured vertebrae	Present study	Alshaali *et al.*[22]
1 vertebra	60.97%	58.8%
2 vertebrae	24.39%	29.4%
3 or more vertebrae	14.63%	11.8%

dicative of osteopenia, and 25% were diagnosed with osteoporosis. In the case of patients with grade 1 fractures, 15% had normal values, 45% had osteopenia, and 40% had osteoporosis. Of the patients with grade 2 fractures, 28% had normal values, 34% had osteopenia, and 38% had osteoporosis. Regarding patients with grade 3 fractures, 38% had normal osteodensitometry values, 35% had osteopenia, and 27% had osteoporosis.

DISCUSSION

Analyzing dorsolumbar spinal radiographs and bone densitometry results in women over 50 years of age, we observed that the number of osteoporosis cases, the number of affected vertebrae, and the degree of severity of vertebral fractures increased with age. We compared our findings with results from other studies in the literature (Table 3).

In the meta-analysis conducted by Yang *et al.*, it was reported that the incidence of osteoporosis ranged from 6% to 57%, with a mean of 31.5%, and that of osteopenia ranged from 25.1% to 58.9%, with a mean of 42%.[21] The frequency of osteoporosis was higher in the study by Alshaali *et al.*, while cases of osteopenia were similar to the data obtained in the present study.[22] In contrast to the findings of Yang *et al.* and Alshaali *et al.*, normal values were more frequently encountered in our study.[21,22] The studies by Alshaali *et al.* and Cai *et al.* yielded different results from ours.[22,23] In the study of Cai *et al.*, the incidence of osteoporosis was 51.19%,[23] compared to our study where it was 31.06%. In the same study, the incidence of osteopenia was 40.2%,[23] which was lower than in our study, at 45.63%.

The study of Kanis *et al.* presents data related to the prevalence of osteoporosis in women over the age of over 50 in 27 European countries, including Romania.[24] According to this study, the prevalence of osteoporosis in Romania is 20.5%, lower than in other Eastern European countries such as Hungary (21.1%), Bulgaria (20.9%), Austria (22.2%), and Slovenia (21.5%). The mean prevalence of osteoporosis in the 27 studied European countries was 22.1%.[24]

A meta-analysis conducted in 2021 by Salari *et al.* reports a prevalence of osteoporosis of 19.8% among European women who participated in the study. On a global scale, across all age groups, this value was found to be 23.1% (Figure 10).[5]

Comparing results from various studies, we observed that the number of cases of osteoporosis associated with the presence of vertebral fractures varies between 29% and 75% (Figure 11). In the study conducted by Cai *et al.*, the incidence of fractures due to osteoporosis was 73.45%, contrasting with our study where this value was significantly lower at 42%.[23] Regarding osteopenia, vertebral deformities were encountered in 22.83% of cases, as opposed

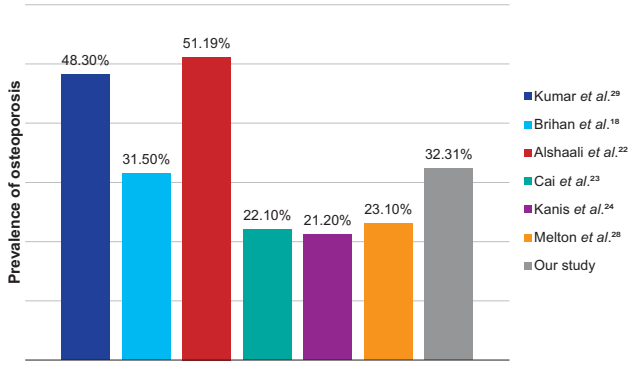

FIGURE 10. Prevalence of osteoporosis

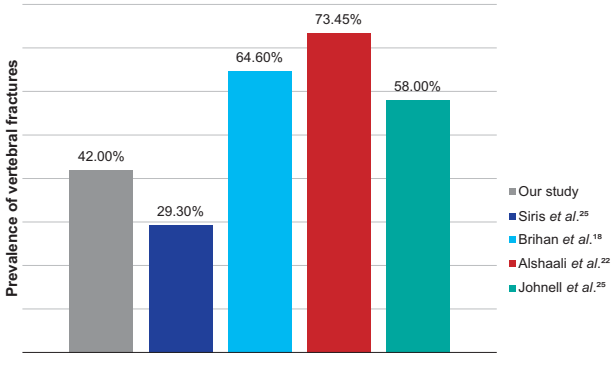

FIGURE 11. Prevalence of vertebral fractures based on bone densitometry

to the cohort analyzed by us, where this value was 30%. The study of Johnell *et al*. reports a prevalence of vertebral fractures of 58% among patients with osteoporosis.[25]

In the case of asymptomatic women, vertebral deformities have been discovered through dorsolumbar spinal radiography or vertebral fracture assessment.[21–23] In the present study, the prevalence of asymptomatic fractures detected through dorsolumbar spinal radiography without undergoing DXA was 16.25%. In the study ofAlshaali *et al*., this figure was 14.2%, in the study of Yang *et al*. it was 28%, and the study of Cai *et al*. it was 31.06%.[21–23] The meta-analysis conducted by Yang *et al*. analyzed multiple cohorts in various geographic regions and reported that in a cohort of 478 postmenopausal asymptomatic women, the incidence of vertebral deformities diagnosed through spinal radiography (lateral incidence) was 29.7%.[21] Similarly to the present study, they observed that the prevalence of fractures in asymptomatic women increased with age. Other studies also demonstrated that most fractures occur in women over the age of 50.[13,21,26,27] According to the study conducted by Melton *et al*., approximately 75% of osteoporosis-related vertebral fractures occur after the age of 65, and compared with our study, it can be observed that although the incidence is on the rise, it is significantly higher beyond this age.[28]

According to several studies, the most frequent fracture sites are the D12 and L1 vertebrae.[18,22,29] Similar results were obtained in the present study. In the study by Alshaali *et al*., the D12 vertebra exhibited deformities in 25% of cases and the L1 vertebra in 21.40%. In comparison, the study by Yang *et al*. did not describe changes in the D12 vertebra, as it focused primarily on pathological alterations in the lumbar spine; however, the L1 vertebra exhibited alterations in 18.37% of cases.[21,22] In the study conducted by Cai *et al*., the D12 vertebra displayed pathological changes in 18.55% of cases, while the L1 vertebra was affected in 17.10% of patients.[23] The number of affected vertebrae in the present study was consistent with that described in the literature (Table 4).

The study by Takahashi *et al*., conducted on a cohort of 185 patients with a mean age of 76.9 ± 7.5 years, suggests that BMD does not decrease in the case of fractured vertebrae, even for patients younger than 75 years.[30] The authors found is no statistically significant association between BMD and the degree of vertebral involvement.[30] The study by Yang *et al*., which predominantly examined morphological changes in the lumbar spine between levels L1 and L4, reported that there was no statistically significant association between mean BMD and the increase in the number of fractured vertebrae.[21]

CONCLUSIONS

In the studied cohort, approximately 25% of patients with normal BMD values exhibited vertebral fractures. Of those without vertebral fractures, approximately 25% had BMD values indicative of osteoporosis. Nearly half of all patients with osteoporosis displayed vertebral fractures. The severity grade of these fractures did not correlate with BMD values. In this context, for the diagnosis of osteoporosis, along with performing bone densitometry, other noninvasive paraclinical investigations, such as spinal radiography, are recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL RESEARCH

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Myocardial Infarction in the Context of COVID-19

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ABSTRACT

Introduction: The COVID-19 pandemic that started in 2019 was a modern-world challenge for medical professionals. The SARS-Cov-2 virus targeted the respiratory and, later, the cardiovascular system. We aimed to identify the risk factors and particularities of acute myocardial infarction associated with SARS-Cov-2 infection. **Material and Methods:** This cross-sectional study included 92 patients admitted to the Cardiology Department of Mureș County Emergency Hospital with myocardial infarction, divided into two groups: 46 patients with COVID-19 and 46 patients without COVID-19. Demographic data, risk factors, non-communicable diseases, and laboratory findings were studied and compared. **Results:** The mean age of the patients was 65 years, and the majority were male. The identified risk factors were hypertension, body mass index >25 kg/m2, and dyslipidemia. The risk factors for poor prognosis were leukocyte count, higher neutrophil-lymphocyte ratio, higher monocyte-to-lymphocyte ratio, and higher high sensitivity troponin I levels. Left ventricular ejection fraction was significantly lower in patients with COVID-19. **Conclusions:** COVID-19 is an aggravating factor of acute myocardial infarction. This research highlights the importance of prevention against the SARS-CoV-2 virus.

Keywords: myocardial infarction, COVID-19, risk factors

INTRODUCTION

In addition to respiratory complications, the cardiovascular system is affected by the SARS-CoV-2 virus by increasing the risk of developing thrombotic incidents: myocardial infarction, pulmonary embolism, and stroke.[1–3] Several studies outlined the risk factors for COVID-19, such as cardiometabolic conditions, age, sex, and ethnicity, some of which can be superposed with the risk factors for cardiovascular diseases.[4,5]

Studies show a less favorable outcome for patients with acute coronary syndrome and COVID-19.[6–9] A concomitant diagnosis of COVID-19 was significantly associated with higher rates of in-hospital mortality compared with patients without a diagnosis of COVID-19.[10] Although acute myocardial infarction rates were lower during the early days of the pandemic, in-hospital and 1-month mortality rates were higher during the year 2020 compared to 2019.[11]

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The hypothesis of this research is based on the presumption that patients with myocardial infarction and COVID-19 infection present with more severe forms of illness, cardiac pump dysfunction, and significantly decreased ejection fraction.

MATERIALS AND METHODS

This cross-sectional study included 92 patients admitted between January 2017 and February 2022 to the Department of Cardiology of Mureș County Emergency Hospital with myocardial infarction. The study population was split into two groups: the COVID group included 46 patients with simultaneous diagnosis of SARS-CoV-2 infection, revealed by typical lesions on the computed tomography (CT) scan, positive RT-PCR test, or COVID-19 antigen rapid test, and the NON-COVID group included 46 patients without evidence of SARS-CoV-2 infection.

Exclusion criteria were systemic diseases, undergoing chemotherapy, cardiotoxic treatment, cardiac devices, and trauma patients. Incomplete files were excluded.

The analyzed parameters included age, sex, body mass index (BMI), personal history of cardiovascular diseases; hypertension, diabetes mellitus, chronic smoking, dyslipidemia; level of serum lipids: cholesterol, triglycerides, routine blood test and number of lymphocytes, thrombocytes, neutrophils, cardiac enzymes: creatine kinase-myocardial band (CK-MB), high sensitivity troponin I (hsTnI), and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Diabetes mellitus was defined as patients having fasting plasma glucose ≥126 mg/dL and/or post-prandial plasma glucose ≥200 mg/dL and/or A1c ≥6.5% or a history of diabetes and/or taking medication for diabetes. Overweight was defined as a BMI >25 kg/m^2 and <30 kg/m^2, whereas obesity was defined as a BMI ≥30 kg/m^2 calculated using Quetlet's formula. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or on antihypertensive treatment. Chronic kidney disease was defined as a glomerular filtration rate (GFR) of <90 mL/min or serum creatinine >1.2 mg/dL. Pulmonary diseases were defined as previously diagnosed by a physician and/or chronic treatment and/or CT scan lesions.

Statistical analysis

Statistical analyses were performed using the demo version of GraphPad and Microsoft Excel. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were given as numbers or percentages. The comparison between groups was done using the Mann–Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. A p value of <0.05 was considered statistically significant.

Ethics

The study was approved by the ethics committee of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology from Târgu Mureș (no. 1659/14.03.2022) and the ethics committee of Târgu Mureș Emergency County Hospital (no. 33208/04.02.2022).

RESULTS

Patients with myocardial infarction and COVID-19 infection were aged between 46 and 76 years, with a mean age of 64.4 years. Of the 46 patients, 33 were female and 13 were male, and 74% survived the illness. Regarding BMI, 83% had a BMI over 25 kg/m^2, and 50% had a BMI over 30 kg/m^2.

Hypertension was observed in 93.47 % (n = 43), 26.08% (n = 12) suffered from diabetes mellitus, and 32.6 % (n = 15) presented with chronic kidney disease. Chronic pulmonary illness affected 48% of patients, and 37% were active smokers at hospital admission. Only 15% of patients presented a history of myocardial infarction. Risk factors are presented in Figure 1.

The mean hospitalization time was 9 days. Most admissions lasted over a week: 8 days for 16 patients (35%) and 11 days for 13 patients (28%). Nine patients (20%) needed more than 2 weeks of hospitalization, and seven were discharged less than a week after admission.

The damage to myocardial tissue is reflected in ejection fraction depression. The study revealed that 58% of the patients who suffered a myocardial infarction and tested positive for COVID-19 had a severe decrease in left ventricular ejection fraction (LVEF) (less than 40%), 32% had an intermediate decrease (between 40% and 49%), and 9% had average ejection fraction.

A total of 38 patients (83%) underwent successful percutaneous transluminal coronary angioplasty (PTCA), and 8 patients (17%) received medical therapy in the form of thrombolysis. A total of 34 patients survived, and 12 patients deceased. Therefore, the survival rate was 74%.

We compared survivor and deceased patients with regards to risk factors, but we found no significant differences (Table 1). However, hospitalization was significantly shorter in the deceased group (p = 0.0056),

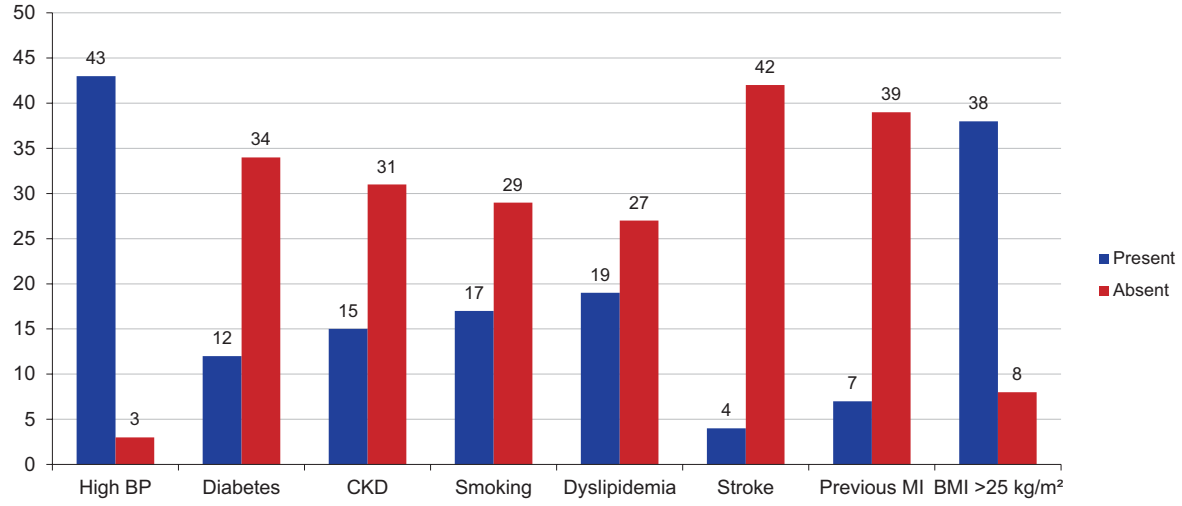

FIGURE 1. Risk factors in myocardial infarction and COVID-19. BP, blood pressure; CKD, chronic kidney disease, MI, myocardial infarction

with a mean of 6 days. The mean BMI was 32.54 kg/m² in the deceased group, higher than in the survivor group (p = 0.0447). hsTnI levels were significantly higher (p = 0.043), while the leukocyte count was significantly lower (p <0.0001) in the survivor group. The neutrophil-to-lymphocyte ratio (NLR) revealed a mild stress level in the survivor group and severe stress in the deceased group (p = 0.0154).

Comparing the two groups, we found significant differences regarding BMI – infected patients had increased body weight, and their heart function was more affected by myocardial infarction – LVEF had a lower value.

TABLE 1. Comparison between deceased and survivors with myocardial infarction and COVID-19

Variable	Survivors	Deceased	p value
Age (years)	63.08 ± 11.77	68.16 ± 14.88	0.2373
Sex			
Female	7	6	0.0699
Male	27	6	
Days of hospitalization	10 ± 4	6 ± 3	0.0056
BMI	29.93 ± 6.72	32.54 ± 3.34	0.0447
Leukocyte count (/mm³)	11,102 ± 3,684	17,284 ± 4,845	<0.0001
NLR	7.39 ± 6.3	14.16 ± 10.5	0.0154
PLR	198.34 ± 133.64	292.37 ± 162.79	0.0541
MLR	0.7424 ± 0.36	1.16 ± 0.82	0.0289
Triglycerides (mg/dL)	153.23 ± 54.7	159.75 ± 45.4	0.72
Colesterol (mg/dL)	143.85 ± 80.16	160.83 ± 50	0.497
NT-proBNP (pg/mL)	6782.11 ± 8129	11524.33 ± 9457.2	0.19
CK-MB (ng/mL)	177.19 ± 162.28	134.91 ± 43.12	0.9354
hsTnI (ng/mL)	9770.476 ± 7816.9	4131.41 ± 2211.7	0.0433
Pulmonary disease			
Yes	19	5	0.5012
No	14	7	
LVEF (%)	38.40 ± 7.488	35.5 ± 5.633	0.2492
Treatment (n)			
PTCA	30	8	0.1778
Medical	4	4	

PLR, platelet-to-lymphocyte ratio

DISCUSSION

This research studied patients suffering from myocardial infarction and COVID-19 infection and found correlations between risk factors, laboratory findings, and myocardial damage following acute coronary events.

COVID-19 infection causes respiratory failure and heart tissue damage; research from the last 3 years outlines the virus' tropism for myocardial tissue.[12,13] LVEF was significantly lower in patients with COVID-19, and there were no significant differences between survivors and deceased patients ($p = 0.2492$), meaning that myocardial damage was present regardless of the clinical outcome.

Increased BMI was a risk factor that presented statistical significance in both comparisons ($p = 0.03$ and $p = 0.04$), suggesting that patients with a higher body weight are more vulnerable to infection, and that an increased BMI is a poor prognostic factor in both myocardial infarction and COVID-19. Increased leukocyte count, NLR, monocyte-to-lymphocyte ratio (MLR), and hsTnI levels were also factors predicting a poor prognosis.

NLR is a prognostic factor used in intensive care that reflects the physiologic stress described by Zahorec *et al.*[14] More recent research by Yang *et al*. highlights the predictive value of NLR as an independent risk factor and high body weight in the context of COVID-19 infection. NLR is a reliable prognostic score in myocardial infarction and COVID-19 infection.[15]

hsTnI levels were significantly lower in deceased patients, which contradicts some of the research indicating it is a marker of cardiac tissue damage. One possible source of error can be the reduced number of subjects included in the study, as data from the literature reflect the results from 525 medical units.[12,13] On the other hand, these numbers can be interpreted in the context that hsTnI peaks 18–24 h from onset and then decreases in the following 2 weeks. Since deceased patients presented a shorter hospitalization and earlier death, the survivors might have presented sepsis and longer, constant cardiac tissue damage, reflected in the elevation of hsTnI.[16] Another hypothesis is that deceased patients were hospitalized earlier for COVID-19, and death may have occurred before the hsTnI peak if the acute coronary syndrome happened during hospitalization. Furthermore, in the presence of multiple chronic illnesses, deceased subjects might have tolerated poorly the myocardial dysfunction and presented earlier to the emergency department compared to survivors, when their hsTnI levels were lower.

CONCLUSION

COVID-19 infection is an aggravating factor of myocardial infarction, and this research outlines the importance of preventive measures in and out of the hospital. Poor prognosis factors identified are leukocyte count, NLR, MLR, level of hsTnI, and increased body weight. Educating the population to reduce cardiovascular risk factors is essential for prevention. However, the COVID-19 pandemic was a test for humanity and forced the medical system to fight and create instruments to treat an unknown disease with yet unknown long-term effects.

CONFLICT OF INTEREST

Nothing to declare.

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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

NEUROSURGERY // PATHOLOGY

A Cadaveric Study of Two Uncommon Cases of Sural Nerve Complex Variation

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ABSTRACT

Introduction: The sural nerve is a sensitive nerve whose function is to provide sensory supply for the posterolateral aspect of the distal third of the leg and the lateral side of the dorsum of the foot. This nerve is formed in the upper third of the calf from the terminal branches of the tibial and common peroneal nerves and the communicating branch of the sural nerve. **Objectives:** The aim of our study is to showcase two anatomical variants of the sural nerve. **Materials and methods:** Two formalin-preserved cadavers, one male and one female, embalmed using formalin 4% were dissected with the intent of being used as teaching materials for the students attending anatomy classes at the “George Emil Palade” University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania. **Results:** In both cases, less common anatomical variations of the formation of sural nerve were discovered. On the male cadaver, we identified the sural nerve as a continuation of the medial sural cutaneous nerve. The lateral sural cutaneous nerve and the communicating branch of the sural nerve were both absent. On the female cadaver, we identified both the medial sural cutaneous nerve and the lateral sural cutaneous nerve. The sural nerve was, however, a continuation of only the lateral sural cutaneous nerve, with the medial sural cutaneous nerve as an independent branch. **Conclusions:** We described two anatomical variants of the sural nerve, which are less common than those documented in the literature.

Keywords: sural nerve complex, variation

INTRODUCTION

The sural nerve, also known as the saphenous nerve due to its course alongside the small saphenous vein in the posterior leg, is a sensitive subcutaneous nerve located in the central axis on the posterior aspect of the calf, between the calcaneal tendon and the lateral malleolus. Its main function is to provide sensory supply for the posterolateral aspect of the distal third of the leg and the lateral side of the dorsum of the foot.[1–4]

In most cases, the sural nerve is formed in the upper third of the calf, from a lateral branch, a medial branch, and the communicating branch of the sural nerve. This anastomosis represents a direct communication between the tibial nerve and the common peroneal nerve.[1,3,5–8] The medial branch is represented

TABLE 1. Variations of sural nerve formation in the literature

Variant	Origin of the sural nerve
A	MSCN (TN) + SCB (SCB arises from LSCN; LSCN arises from CPN)
B	MSCN (TN) + SCB (LSCN and SCB arise from the bifurcation of a CPN branch)
C	MSCN (TN) + SCB (SCB and LSCN arise independently from CPN)
D	MSCN (TN) + SCB (SCB arises from CPN; LSCN arises from SCB)
E	MSCN + SCB (SCB arises from CPN; absent LSCN)
F	MSCN (TN) (SN is a continuation of MSCN; absent LSCN and SCB)
G	MSCN (TN) (SN is a continuation of MSCN; independently present LSCN; absent SCB)
H	MSCN (TN) arises from SCB (distal third of the leg); SN is a continuation of LSCN (CPN)
I	MSCN (TN) independently present, up to the heel; SN is a continuation of LSCN (CPN); absent SCB
J	MSCN (two independent branches from TN: TCB1 + TCB2); SN is a continuation of MSCN; absent LSCN and SCB
K	MSCN (two independent branches from TN: TCB1 + TCB2); SCB arises from LSCN
L	MSCN (TN) + NFCP; independent LSCN; absent SCB
M	MSCN (SCN); SN is a continuation of MSCN; absent LSCN and SCB
N	SCB arises from MSCN (TN) (proximal third of the leg); SN = SCB + LSCN (CPN)
O	Independent MSCN (TN) present up to the proximal third of the leg; SN is a continuation of LSCN (CPN); absent SCB
P	SN is a continuation of LSCN (CPN); absent MSCN

SN, sural nerve; SCN, sciatic nerve; LSCN, lateral sural cutaneous nerve; MSCN, medial sural cutaneous nerve; SCB, sural communicating branch; LDCN, lateral dorsal cutaneous nerve; TN, tibial nerve; CPN, common peroneal nerve; PCFN, posterior femoral cutaneous nerve; TCB, tibial connection branch

by the medial sural cutaneous nerve (MCSN), which originates from the tibial nerve (L4–S3) and descends between the two heads of the gastrocnemius muscle towards the central axis of the calf. After perforating the crural fascia, it joins the communicating branch of the sural nerve.[2,3,7,9] The lateral branch, known as the lateral sural cutaneous nerve (LCSN), is a branch of the common fibular (peroneal) nerve (L4–S2), which emerges in the lateral side of the popliteal fossa. The communicating branch of the sural nerve originates from the common peroneal nerve or the lateral branch root of the common peroneal nerve and anastomoses with the medial sural cutaneous branch in the upper third of the calf.[1,3,7,9]

Numerous anatomical variants have been described in the literature regarding the origin and course of the sural nerve (Table 1, Figure 1). Variations most commonly arise based on the presence or absence of the communicating branch of the sural nerve, which may be missing, have different origins, or even be supernumerary. Variants have been described where the MCSN or the LCSN is missing or does not participate in the formation of the sural nerve. The sural nerve branching from the tibial nerve superior to the popliteal fossa or from the sciatic nerve are among the less common variations.[1,4,8]

The sural nerve is used as a graft site for the reconstruction of other peripheral nerves and for the diagnosis of various neurologic diseases through biopsy. Therefore, a comprehensive understanding of the level of formation, course, length, and proximity of the sural nerve to the small saphenous vein, gastrocnemius muscle, and calcaneal tendon are essential for both surgical and clinical practice.[2,5,8,10–13] The aim of our study is to showcase two anatomical variations in the formation of the sural nerve and to provide further data in regards to the incidence of certain variants.

MATERIALS AND METHODS

We used two formalin-preserved cadavers, one male and one female, embalmed using formalin 4%. Both were dissected with the intent of being used as teaching material for the students attending anatomy classes at "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania. In both cadavers, dissection was performed only on the left lower limb, as the contralateral leg was missing due to previously being amputated superior to the popliteal fossa. Therefore, comparative dissection could not be performed.

Ethics

This study was approved by the ethics committee of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (no. 2366/06.06.2023).

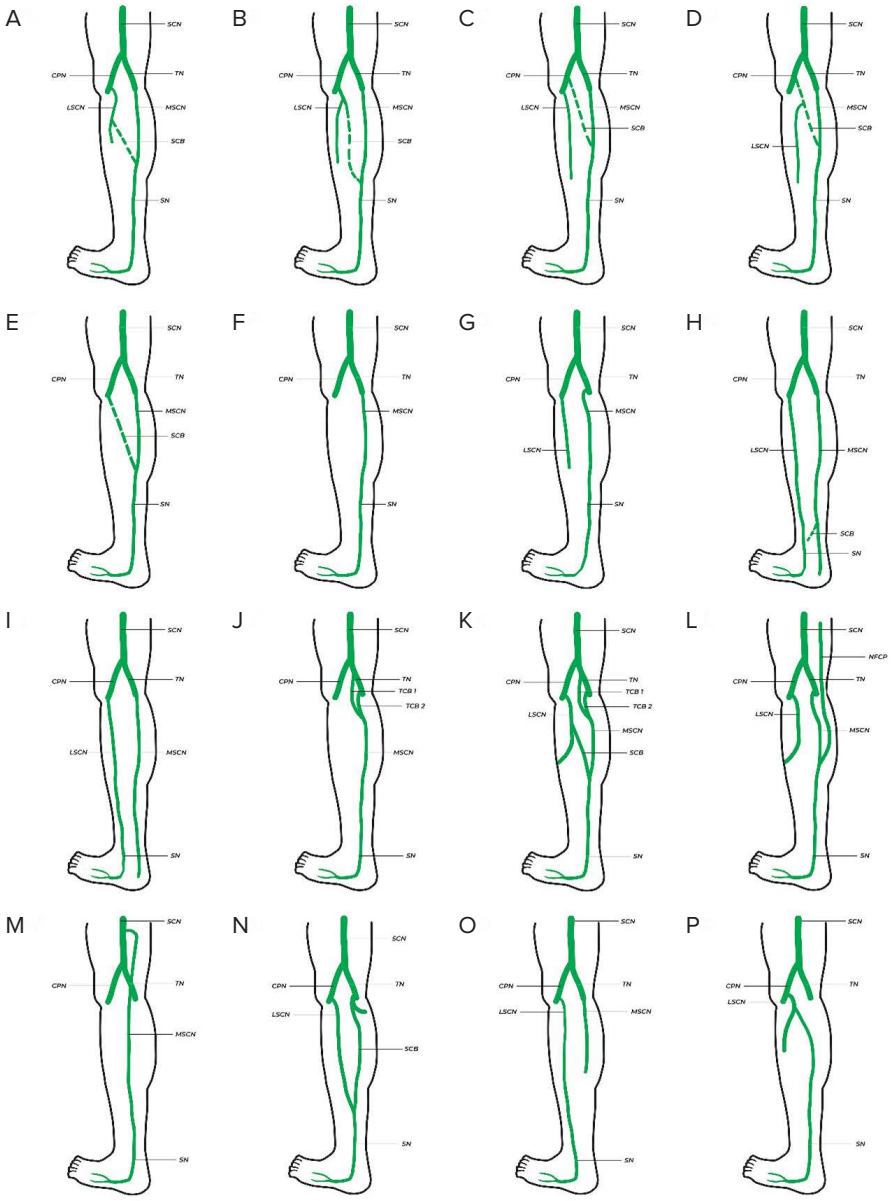

FIGURE 1. Formation and course variants of sural nerve as described in the literature

RESULTS

On the male cadaver, we identified the sural nerve as a continuation of the MCSN. The lateral sural cutaneous nerve and the communicating branch of the sural nerve were both absent. On the female cadaver, we identified both the MSCN and the LSCN. The sural nerve was however, in this instance, a continuation of only the LSCN, with the MSCN as an independent branch, and the communicating branch was completely missing.

DISCUSSION

The sural nerve is commonly used as a harvesting site for nerve grafts, being essential for in the reconstruction of various peripheral nerves. Maxillofacial surgery makes use of these nerve grafts when reparation of the facial or inferior alveolar nerve is required after tumor extirpation or bone reconstruction. The removal of invasive retroperitoneal or pelvic tumors often also targets adjacent nerves, and the sural nerve can be used for ilioinguinal, femoral, or sciatic nerve reconstruction. It is also used in the diagnosis of pathologies associated with neurological damage such as diabetic neuropathy or acute inflammatory polyradiculoneuropathy (Guillen-Barré disease), both through electrophysiological studies and through its biopsy.[2,5,8,10–13]

Multiple variants of the formation of the sural nerve have been documented in the literature. A study performed by Steele *et al*. on a group of 208 lower limbs described a total

TABLE 2. Statistical distribution of sural nerve formation variants, according to the literature

Study	Variant (%)								
	A	B	C	D	E	F	G	H	I
Ramakrishnan *et al.*[7]	51.5				13.8	31.2			
Steele *et al.*[1]	12.02	13.46	7.69	8.17	8.65	8.65	25.96	10.58	3.85
	41.34					34.61			
Jeon *et al.*[2]	1.73				78.03	8.67		3.46	
Riedl *et al.*[14]	46.66	10	6.66			6.66	2.66		3.33
Büyükmumcu *et al.*[15]	35.83				34.16	20.83		4.16	
Our cases						50			50

of 11 variants of formation of the sural nerve complex.[1] The most frequent patterns were type G, (n = 54; 25.96%), type B (n = 28; 13.46%), and type A (n = 25; 12.02%) (Table 2).

Studies conducted in our geographical area, such as those by Riedl *et al.* and Büyükmumcu *et al.*, show variant A as the most common, representing 46.66% and 35.83% of the total cases studied, respectively.[14,15] In contrast, in the study of Jeon *et al.*, only 1.73% of the studied lower limbs presented this variant of sural nerve formation.[2]

In a meta-analysis performed by Ramakrishnan *et al.*, variants A, B, C, and D were grouped together and were present in 51.5% of the total cases described.[7] In the study of Steele *et al.*, these variants were described separately, the sum of their incidences being 41.34%, with a relatively small difference compared to the previous study.[1,8]

More notable differences were found in the case of type E. It was found to be rarer in the studies conducted by Steele *et al.* and Ramakrishnan *et al.*, with an incidence of 8.65% and 13.8%, respectively.[1,7] In contrast, Jeon *et al.* found this variant in 78.03% of cases.[2] In the study of Büyükmumcu *et al.*, type E was the second most frequent variant, with an incidence of 34.16% of the total dissected preparations.[15]

In this study, we described two anatomical variants of the sural nerve. In the lower left limb of a male corpse, we identified variant F, the sural nerve being present as a continuation of the MCSN, while the LSCN and the sural communicating branch were both absent. In the lower left limb of the female corpse, we identified variant I, in which the sural nerve was a continuation of the LSCN branch, and no apparent communication with the MSCN branch was present.

Similar to our case, Steele *et al.* found variant F of sural nerve formation (Figure 2) in 18 lower limbs (8.65%) in the studied group.[1] Studies conducted in our geographical area, show variant F to be present in 6.66% and 20.83% of

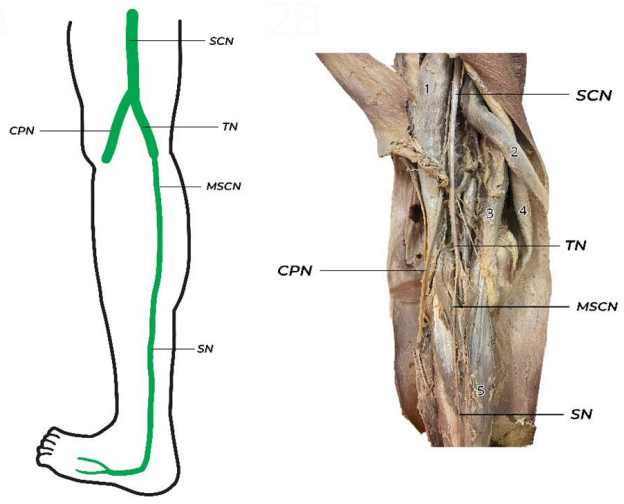

FIGURE 2. Variant F. 1 – Biceps femoris muscle; 2 – Semitendinosus muscle; 3 – Semimebranosus muscle; 4 – Gracillis muscle; 5 – Gastrocnemian muscle.

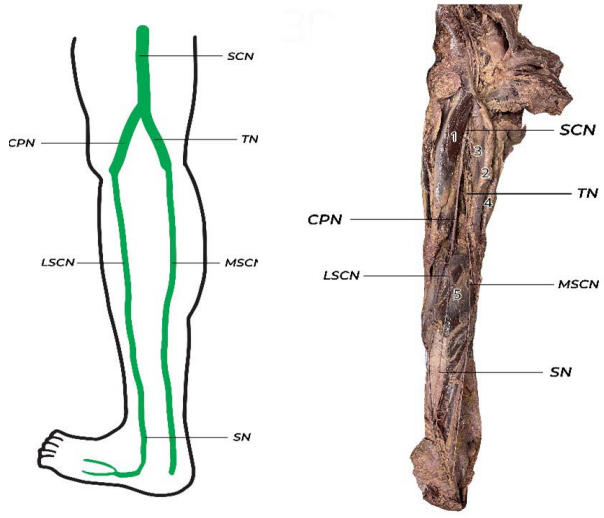

FIGURE 3. Variant I. 1 – Biceps femoris muscle; 2 – Semitendinosus muscle; 3 – Semimebranosus muscle; 4 – Gracillis muscle; 5 – Gastrocnemian muscle.

cases, respectively.[14,15] In the group studied by Steele *et al.* in the USA, type F proved to be a rare variant, with an incidence of 8.65%.[1]

Variants F and G described in the meta-analysis of Ramakrishnan *et al.* represented 31.2% of the studied group. Variant I (Figure 3), also described in this study, was found in approximately equal proportions by Steele *et al.*, Jeon *et al.*, and Riedl *et al.*, with an average incidence of 3.54%.[1,2,7,8,14,15]

Among the extremely rare variants (n = 1; 0.48%) described by Steele *et al.* are variants O and P, currently not included in the classification system and not discussed separately in the study of Ramakrishnan *et al.*[7] Similarly, very rare and still unrecognized variants were also identified by Büyükmumcu *et al.*, such as type J (n = 2; 2.5%), type K (n = 1; 0.83%), or L (n = 1; 0.83%).[1,7,14,15]

CONCLUSIONS

Taking into consideration the role of the sural nerve in regards to peripheral nerve reconstruction using grafts, the importance of being aware of its variants cannot be denied. In this study, we described two of the less common variants, type F and type I.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL RESEARCH

GYNECOLOGY // MACHINE LEARNING

Digitization of Gynecology Using Artificial Intelligence: Cervical Mapping Corroborated With Clinical Data for Conization Necessity

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ABSTRACT

Background: Cervical cancer is the fourth most common female malignancy worldwide. In developing countries, it is the most common subtype of cancer and the third leading cause of cancer mortality among women. Artificial intelligence has the potential to be of real use in the prevention and prompt diagnosis of cervical cancer. The aim of our study was to develop a medical platform consisting of an automated observation sheet containing colposcopy data, a software that would use a machine learning module based on clinical and image data for diagnosis and treatment, and a telemedicine module to enable collaboration between gynecologists. **Materials and methods:** Clinical and colposcopy image data from 136 patients were introduced into a machine learning module designed to generate an algorithm for proposing a preliminary diagnosis and treatment. The clinical and imaging data were corroborated to generate six options: 'Follow-up', 'Pharmacotherapy', 'Biopsy', 'Curettage', 'DTC', and 'Conization'. **Results:** Data generated by the machine learning module regarding treatment options were compared with the opinion of gynecologists and yielded an accuracy of 78% for 'Follow-up', 81% for 'Pharmacotherapy', 84% for 'Biopsy', 90% for 'Curettage', 96% for 'DTC', and 81% for 'Conization'. **Conclusions:** The developed software can be an important step towards the digitization of existing gynecology offices and the creation of intelligently automated gynecology offices related to prevention and treatment of cervical cancer. More data is needed to improve the accuracy of the developed software.

Keywords: cervical cancer, colposcopy, human papilloma virus, machine learning, artificial intelligence

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INTRODUCTION

Cervical cancer (CC) is the fourth most common female malignancy worldwide.[1] In developing countries, it is the most common subtype of cancer and the third leading cause of cancer-related mortality among women. One of the most important discoveries in the etiological investigation of cancer in the last 25 years was that CC is caused by persistent infection by certain genotypes of human papillomavirus (HPV).[1-3] Accumulating scientific evidence from virological, molecular, clinical and epidemiological studies has unequivocally demonstrated that CC is in fact a consequence of long-term unresolved infection with certain HPV genotypes. Thus, we can state that CC is the result of a viral infection, and preventing and treating the infection at the right time is the most important strategy to consider in the primary prevention of CC and other diseases caused by HPV. More than 95% of cervical cancers (squamous cell carcinomas and adenocarcinomas) have been attributed to infection with high-risk HPV strains including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (these viruses are assigned by the IARC to Group 1). However, the most common (~70%) strains involved in cervical carcinogenesis are HPV 16 and 18.[1–3]

HPV infection is basically a sexually transmitted disease. As such, both men and women are involved in the epidemiological chain of infection. There are asymptomatic carriers, transmitters, and victims of HPV infection simultaneously.[1–5] In this sense, the risk factors associated with HPV infection are clearly related to the individuals' sexual behavior. Epidemiological and clinical studies incorporating high-sensitivity molecular biology techniques in biological specimens have detected oncogenic or high-risk HPV in almost all cases of CC. HPV DNA is detected in most (70–90%) precursor lesions or high-grade intraepithelial lesions (CIN II–III) and in a smaller fraction (20–50%) in low-grade lesions (CIN I) as well.1-3 However, it is also worth mentioning that in the category of cytological lesions of uncertain nature (ASCUS and AGUS) the HPV infection rate is close to 50%.[1]

Another important aspect from an epidemiological point of view is the association of Epstein–Barr virus (EBV) and HPV co-infection with the development of CC. Even if this correlation is not very obvious, there are numerous studies that draw attention to this aspect. EBV co-infection with HPV confers a four-fold increased risk of CC in EBV-positive women.[1] Similarly, precancerous cervical lesions are twice as common in EBV-positive women compared to EBV-negative cases.[4] These data point to EBV as a potentially active cofactor in the pathogenesis and progression of CC. The presence of EBV in the cervix may also accelerate the integration of HPV genome into the genome of cervical cells, increasing the genomic instability of infected cervical cells. In addition, chronic cervicitis may also facilitate EBV infection and its potential oncogenic effects. These viruses, alone or in collaboration, can induce oncogene activation and epithelial–mesenchymal transition, one of the key steps in tumor progression and metastasis.[5] Based on the analyzed studies, we can draw the conclusion that this area of research represents a worldwide discussion.[4–19]

Colposcopy is often used as a follow-up procedure when a Pap smear (Pap test) indicates abnormal cervical cells. The colposcope allows the healthcare provider to visualize the cervix more clearly and identify areas of concern that may require further evaluation or treatment. Colposcopy can help in identifying and diagnosing various cervical abnormalities such as cervical dysplasia, HPV infection, and cervical inflammation.[20] Colposcopy is also used to monitor the effectiveness of treatment for cervical abnormalities. After treatment, regular colposcopy examinations can help ensure that the treated area is healing properly and that no further abnormalities are present. Colposcopy can also guide surgical procedures aimed at removing abnormal tissue. It can be clearly stated that colposcopy images are crucial in the diagnosis of CC.[20–23]

The main purpose of this study was the digitization of gynecology clinics by developing a software that would aid the recognition of malignant and premalignant lesions caused by CC. Our aim was to develop a digital platform that is useful for gynecologists from several points of view and contain the following: 1) an online medical record containing colposcopy data that can be filled out quickly and easily, acting as an automated observation sheet that generates highly accurate statistical data both for medical practice and for clinical studies; 2) a software for establishing preliminary diagnosis and treatment; 3) a telemedicine module.

MATERIALS AND METHODS

Development of an automated medical record platform with telemedicine module

In the first stage, an observation sheet regarding CC was created, containing the following data: age; reason of examination; antecedents for cytology, HPV infection, colposcopy, cervical biopsy, and conization; current colposcopy results; squamous-cylindrical junction: upper limit, transformation zone; abnormal aceto-white area: aceto-white epithelium, punctations, mosaic, leukoplasia, mi-

croinvasion, invasion, Schiller test, iodine negative areas, iodine negative areas corresponding to aceto-white epithelium, contour of iodine negative areas, atypical vessel, other aspects (polyp, vegetation, condyloma, leukoplasia, adenosis, inflammation, atrophy, stenosis, Nabothian cyst, ulceration); SWEDE score; diagnosis, recommended treatment. An automated medical record platform was created based on this observation sheet.

The software was developed using clinical and colposcopy data from the medical records of 136 patients admitted to the Clinica Avicena Profertis gynecology hospital in Iași, Romania. As the software is intended for the recognition of malignant and premalignant lesions necessary for a preliminary diagnosis and treatment, the clinical data were introduced into a machine learning module. All data were anonymized according to the legislation in force. A telemedicine module entitled 'Cervix map' was added to the platform, allowing collaboration and opinion exchange between doctors.

Development of the software

The developed software is based on a machine learning module. The development included two stages: 1) feature extraction from clinical data; 2) feature extraction from colposcopy images.

Feature extraction from clinical data

In the first stage, clinical data extracted from the medical records were introduced into a machine learning module for training purposes. The module was designed to generate an algorithm for proposing a preliminary diagnosis and treatment. For this purpose, we trained decision tree and random forest machine learning models. Based on the data from the observation sheets, the module provides six treatment options: 'Follow-up', 'Pharmacotherapy', 'Biopsy', 'Curettage', 'DTC' (diathermocoagulation), and 'Conization/LLETZ' (large loop excision of the transformation zone). In the first step, the module generates a decision tree for each of the six options. Figure 1 presents the decision tree generated for conization/LLETZ.

In the case of random forest models, the weight of each input parameter can be visualized. The results generated by this method are based on the importance of features for each of the six options mentioned above. Random forest models generated for follow-up and pharmacotherapy are presented in Figure 2 and for DTC and conization in Figure 3.

Feature extraction from colposcopy images

At this stage, our goal was to collect a large set of colposcopy images. We collected a set of 550 colposcopy images from

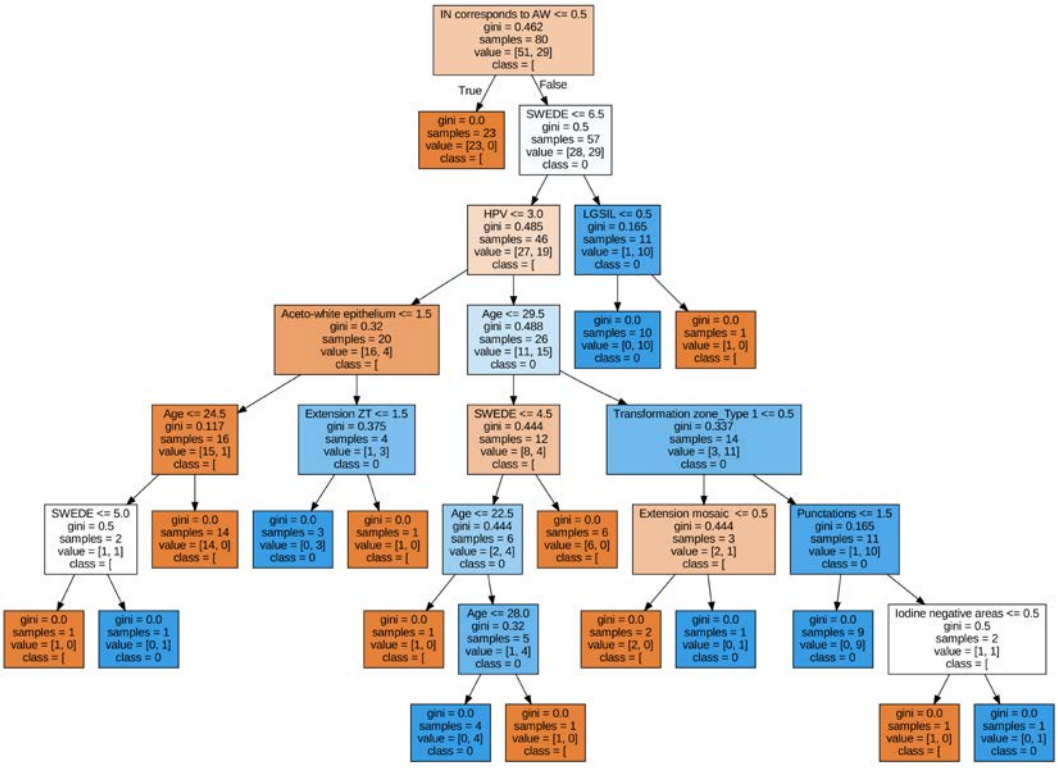

FIGURE 1. Decision tree for conization/LEETZ

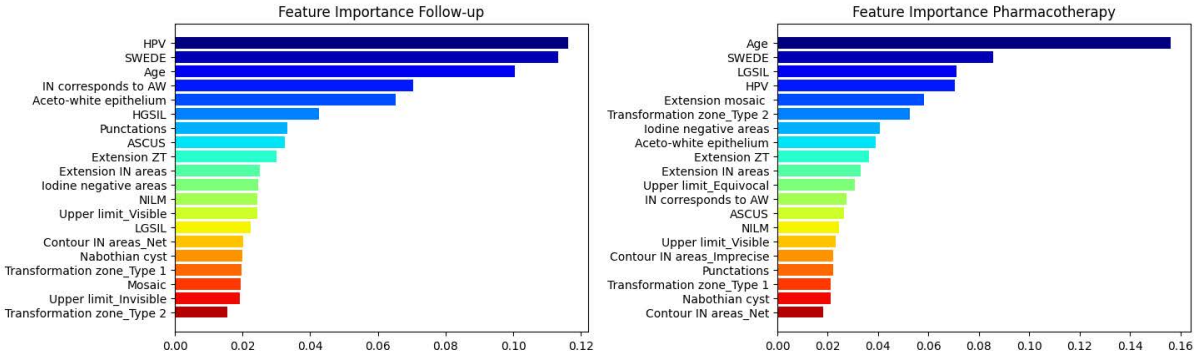

FIGURE 2. Random forest model for follow-up and pharmacotherapy

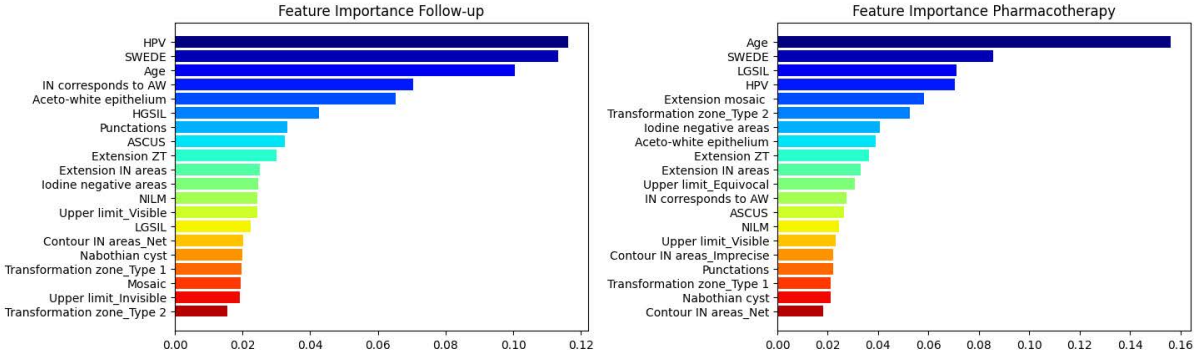

FIGURE 3. Random forest model for DTC and conization

the 136 medical records included in the study. In order to be able to differentiate between healthy tissues and pathological changes of the cervical tissue, the images were manually segmented and annotated by specialists. The segmentation used the following colors codes: blue for the squamous-cylindrical junction; purple for the aceto-white area; red for atypical vessels, punctations, and mosaic; yellow for Naboth cysts; black for cuffed gland opening; and white for leukoplasia. Examples of segmented images are presented in Figure 4. The segmented and annotated images were added to the machine learning module, and the features were corroborated with the clinical data obtained from the medical records.

Ethics

The study was conducted in accordance with the principles stated in the Declaration of Helsinki and was approved by the ethics committees of the institutions the authors are affiliated with.

RESULTS

Data generated by the machine learning module regarding treatment options were compared with the opinion of gynecologists based on the segmented and annotated colposcopy images. Statistical analysis yielded the following results regarding the accuracy of the developed algorithm in suggesting a preliminary treatment: 78% for 'Follow-up', 81% for 'Pharmacotherapy', 84% for 'Biopsy', 90% for 'Curettage', 96% for 'DTC', and 81% for 'Conization'.

DISCUSSION

Colposcopy is crucial for the diagnosis of CC, and prevention and prompt diagnosis are of major importance. In this field, artificial intelligence proves to be of real use – the developed automated medical record platform with telemedicine could be important for physicians. In order to develop a lesion recognition software that is capable of establishing a preliminary diagnosis and treatment is important to corroborate clinical data with colposcopy image data. Of note, in our dataset the number of features was close to the number of records. As a consequence, machine learning models might find correlations between the output (treatment) and certain features that are irrelevant from a medical point of view. These correlations could be coincidences that exist only in this dataset, meaning that much more data is needed to increase the reliability of our models.

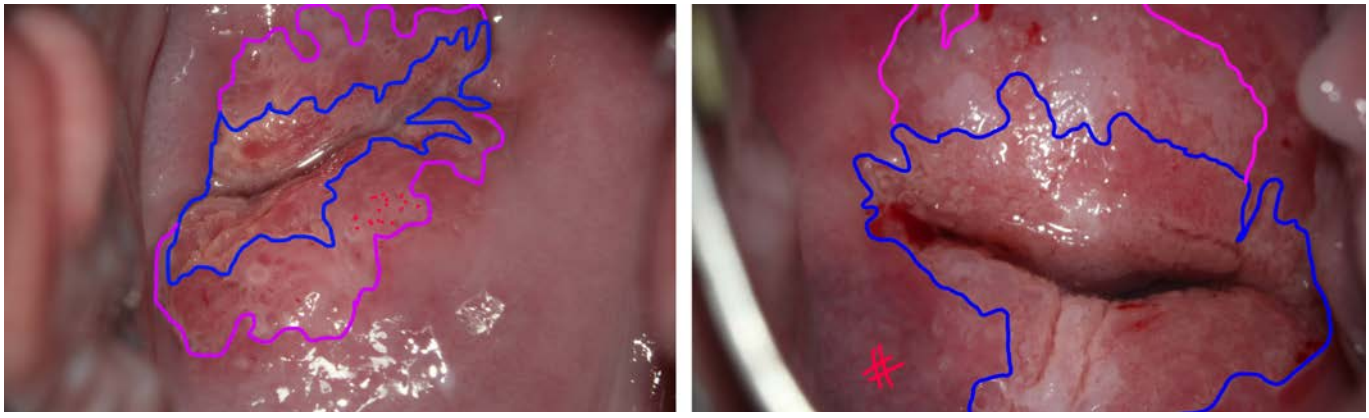

FIGURE 4. Segmented colposcopy images

CONCLUSIONS

The developed software can generate an algorithm for establishing a preliminary diagnosis and treatment. To increase the prediction accuracy of this software, it is necessary to collect a larger volume of data, taking into account in particular the corroboration of clinical data and colposcopy images. Our intention is to further develop this software We consider our software to be an important step towards the digitization of existing gynecology offices and the development of intelligently automated gynecology offices related to the prevention and treatment of CC. We intend to collect more data and improve the accuracy of this software.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CASE REPORT

INTERNAL MEDICINE // HEMATOLOGY

Sweet Syndrome in a Patient with Acute Leukemia on Azacitidine and Venetoclax Treatment

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ABSTRACT

Introduction: Sweet syndrome, also called acute febrile neutrophilic dermatosis, is a rare disorder characterized by skin lesions accompanied by high fever and elevated inflammatory markers. **Case Presentation:** In January 2023, a 73-year-old Caucasian male was diagnosed with acute myeloblastic leukemia and subsequently chemotherapy with azacitidine and venetoclax was initiated. One week after the second round of chemotherapy with azacitidine, the patient developed a fever of 39°C. Physical examination revealed purple plaques on the skin of the head, neck, and arms associated with pain but not itching. Initially, the plaques appeared at the site of the subcutaneous azacitidine injection (left upper extremity) and then began to spread. The infectious diseases consultation established the diagnosis of multiple abscesses. Antibiotic therapy was initiated with meropenemum and linezolidum, and later colistin was associated, but the skin lesions and the patient's condition worsened. A dermatology consultation was performed, which established the diagnosis of Sweet syndrome, and subsequently corticosteroid therapy was started. The skin lesions started to improve after 3 days. **Conclusions:** Sweet syndrome is a rare condition that is difficult to diagnose because of the wide spectrum of differential diagnoses.

Keywords: Sweet syndrome, acute febrile neutrophilic dermatosis, acute myeloblastic leukemia, azacitidine

INTRODUCTION

Sweet syndrome, also called acute febrile neutrophilic dermatosis, is a rare disorder affecting the skin and mucosae. It is characterized by skin lesions accompanied by high fever and elevated inflammatory markers.[1]

The etiology of Sweet syndrome may be idiopathic or secondary to an underlying condition such as infection, autoimmune disease, or malignancy. In addition, Sweet syndrome may be induced by medication such as contraceptive drugs, chemotherapy, granulocyte colony-stimulating factor (G-CSF) or

TABLE 1. Laboratory investigations

	Initial laboratory examination	Laboratory investigations after the second round of azacitidine	Laboratory investigations at the onset of Sweet syndrome
White blood cells, /mm^3	1,360	1,070	1,290
Neutrophiles, /mm^3	530	340	1,010
Lymphocytes, /mm^3	740	700	250
Monocytes, /mm^3	90	20	30
Basophils, /mm^3	0	0	0
Eosinophils, /mm^3	0	1	0
Hgb, g/dL	6	8.2	5.7
Htc, %	17.3	23.2	16.5
Platelets, /mm^3	31,000	21,000	123,000
Erythrocyte sedimentation rate, mm/h	40	30	87

granulocyte-macrophage colony-stimulating factor (GM-CSF), non-steroidal anti-inflammatory drugs (NSAIDs), or vaccination.[2]

We hereby report a case of a patient who was diagnosed with acute myeloblastic leukemia (AML) in January 2023, started treatment with azacytidine and venetoclax, and developed Sweet syndrome.

CASE PRESENTATION

In January 2023, a 73-year-old Caucasian male, diagnosed with myelodysplastic syndrome in 2022, presented to the emergency department for severe asthenia and fatigue. The initial laboratory examination revealed severe pancytopenia (Table 1), therefore the patient was admitted to the Hematology Department of the Emergency County Clinical Hospital of Târgu Mureș, Romania.

Blood smear revealed 2% blasts, anisocytosis, macrocytes, ovalocytes, and a low platelet count. Bone marrow aspiration revealed 52% blasts with an immunophenotype consisting of AML with aberrant CD4 and CD22 markers and negative myeloperoxidase.

Because the patient was not a candidate for intensive induction therapy, chemotherapy with azacitidine and venetoclax was initiated according to international protocols.3 After the first round of chemotherapy, venetoclax was discontinued due to severe pancytopenia. One week after the second round of chemotherapy with azacitidine, the patient developed a fever of 39°C at home and was admitted to the hematology department on an emergency basis. Physical examination revealed tender, swollen violaceous plaques and nodules on the skin of the head, neck, and arms associated with pain but not itching (Figures 1, 2, and 3). Initially, the plaques appeared at the site of the subcutaneous azacitidine injection (left upper limb) and then began to spread (Figure 1). Laboratory examination revealed leukopenia, anemia, and severe systemic inflammation (Table 1).

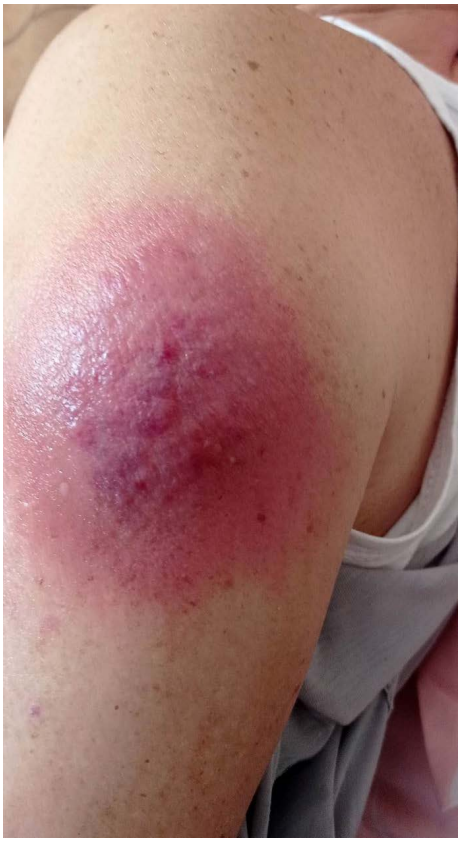

FIGURE 1. Left upper limb: tender, swollen violaceous plaque the site of the subcutaneous azacitidine injection

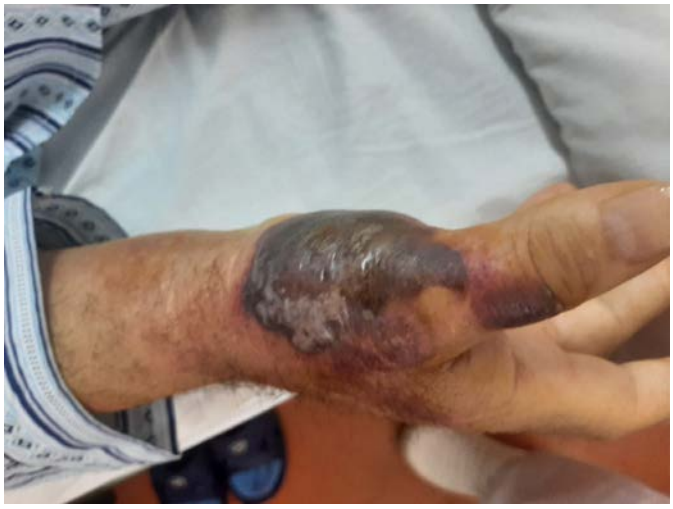

FIGURE 2. Tender, swollen violaceous plaques on the left hand

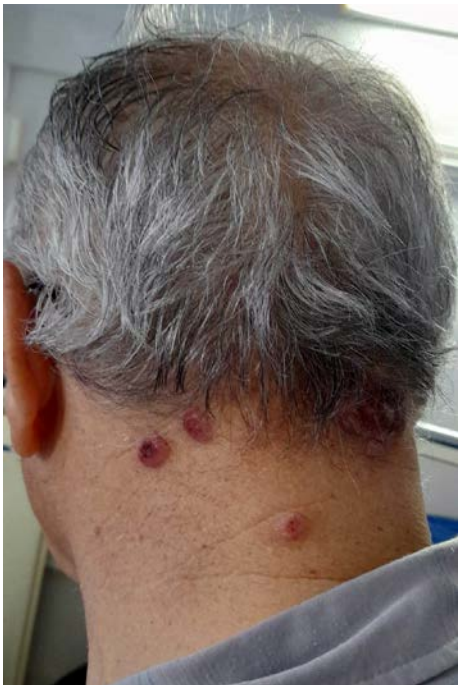

FIGURE 3. Tender, swollen violaceous nodules with hematic crust on the back of the neck

An infectious diseases consultation was performed, which established the diagnosis of multiple abscesses and recommended hemocultures and bacteriological examination of secretions from the abscesses, as well as antibiotic therapy with meropenemum and linezolidum. After three days, another infectious diseases consultation was required because the skin lesions worsened and widened, and inflammatory markers increased. It was recommended to continue treatment with meropenemum and linezolidum and to add colistin to the therapeutic regimen. The results of hemocultures and bacteriological examination of secretions from the abscesses were negative. The patient's condition deteriorated visibly with persistent fever, further extension of the skin lesions, and a further increase in in-

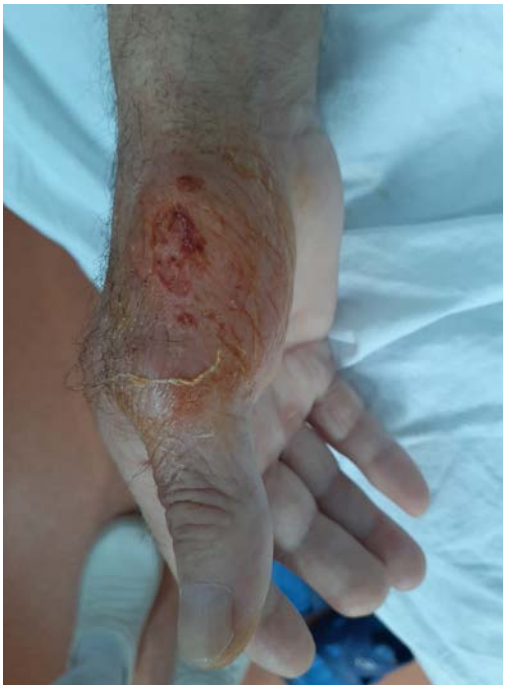

FIGURE 4. The left hand after 3 days of corticosteroid therapy. The violaceous plaque disappeared, being replaced by an ulcerative lesion

FIGURE 5. The left hand after 3 days of corticosteroid therapy. The violaceous plaque disappeared, being replaced by an ulcerative lesion

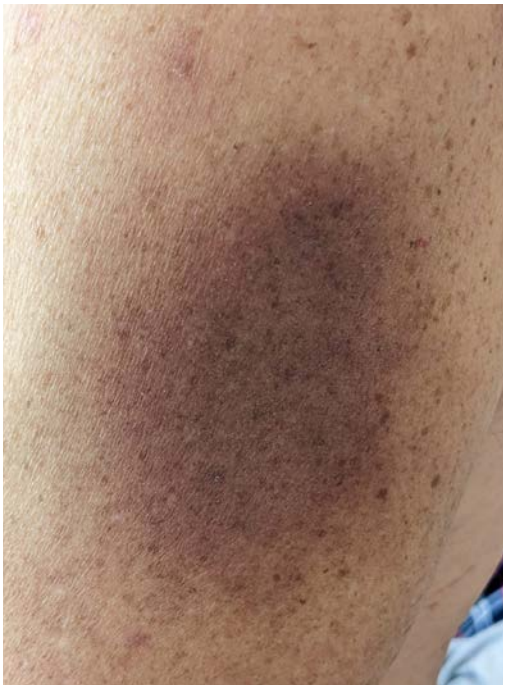

FIGURE 6. The site of the subcutaneous azacitidine injection on the left upper limb after 3 weeks, showing the complete resolution of the plaque, which was replaced by a brown cicatrice.

flammatory markers, prompting another infectious diseases consultation, which this time suggested the diagnosis of pyoderma gangrenosum and recommended consultation with a dermatologist. The dermatology consultation established the diagnosis of Sweet syndrome and recommended a biopsy and intravenous corticosteroid therapy. The patient refused the biopsy. Corticosteroid therapy was started with intravenous methylprednisolonum 0.5 mg/kg in gradually decreasing doses in association with antibiotics and antifungal therapy. After three days, the skin lesions began to improve (Figure 4), and laboratory testing prior to discharge revealed an erythrocyte sedimentation rate of 23 mm/h. For the following rounds of chemotherapy, azacitidine was replaced with decitabine, which was well tolerated. Figure 5 and Figure 6 show the lesions almost 3 weeks after the diagnosis of Sweet syndrome has been established.

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Emergency County Clinical Hospital of Târgu Mureș (12357/19.05.2023). The patient signed an informed consent on admission regarding anonymous data collection for scientific purposes.

DISCUSSION

Sweet syndrome was first described in 1964 by Dr. Robert Douglas Sweet in England as 'acute febrile neutrophilic dermatosis' in eight patients, all women, with the same constellation of pathologic signs and symptoms: "fever, neutrophil polymorphonuclear leukocytosis of the blood, raised painful plaques on the limbs, face, and neck, and histologically a dense dermal infiltration with mature neutrophil polymorphs".[4]

The pathophysiology of Sweet syndrome is unknown. There are many theories, the most reliable is related to type III hypersensitivity reaction, but also to overproduction and inadequate regulation of inflammatory cytokines such as G-CSF, GM-CSF, interleukin (IL)-1, IL-3, IL-6, and IL-8.[5,6] Classically, Sweet syndrome is characterized by fever, leukocytosis, and tender erythematous skin lesions (papules, nodules, and plaques) that usually respond rapidly to corticosteroid therapy.[7]

Drug-induced Sweet syndrome can be triggered by many drugs, but the most common cases were reported in association with G-CSF, retinoids, azathioprine, and sulfamethoxazole and trimethoprim.[7,8] The temporal relationship between azacitidine administration and the appearance of the Sweet syndrome lesions, as well as the absence of relapse after discontinuation of the drug suggest a drug-related etiology.

Approximately 20% of Sweet syndrome cases are associated with malignancies and up to 80% with hematologic disorders,[9] the most common of which are AML and myelodysplastic syndrome (MDS).[10] Studies suggest that the association of Sweet syndrome and MDS has a poor outcome.[9] In 2015, Kazmi *et al.* conducted a retrospective study demonstrating that 1% of patients with AML develop Sweet syndrome.[11]

The differential diagnosis of Sweet syndrome includes various diseases (Table 2).[12,13] Because of the similarity between Sweet syndrome and necrotizing infections, diagnosis may be difficult and may delay the initiation of corticosteroid treatment,[14] as demonstrated by our case in which the diagnosis and treatment were postponed due to a misdiagnosis of multiple abscesses, and treatment was started with antibiotics that the patient did not respond to. As it can be observed in the pictures, the patient responded very quickly to corticosteroid therapy and the lesions began to heal the very next day.

Sweet syndrome can also represent a rarely reported side effect of azacitidine treatment. According to the literature, the time frame between azacitidine administration and the appearance of Sweet syndrome varies from 5 days to 9 months.[15] Studies also suggest that patients in whom Sweet syndrome occurred in association with azacitidine treatment had leukopenia.[6,16] Although Sweet syndrome is classically associated with leukocytosis,

TABLE 2. Differential diagnosis of Sweet Syndrome[12,13]

Clinical	Cellulitis Erysipelas Allergic contact dermatitis Herpes simplex Leprosy
Neutrophilic dermatosis	Pyoderma gangrenosum Behcet's disease Bowel associated dermatitis arthritis syndrome
Cutaneous vasculitis	Erythema elevatum diutinum Cutaneous polyarteritis nodosa granuloma faciale Cockade purpura
Reactive erythemas	Annular urticaria Erythema multiforme
Panniculitis	Lupoid panniculitis Erythema nodosum
Granulomatous disorders	Sarcoidosis Inflammatory granuloma annulare Palisaded neutrophilic granulomatous dermatitis
Histopathological	Leukemia cutis Neutrophilic eccrine hidradenitis Leukocytoclastic vasculitis
Others	Eosinophilic cellulitis (Wells syndrome)

most patients are known to develop leukopenia after chemotherapy.[17]

In 2012, Trikett *et al.* reported two cases of azacitidine-related Sweet syndrome and claimed that by that time, only three other cases of azacitidine-related Sweet syndrome had been reported in the United States.[18] In 2015, Troccola *et al.* reported the case of a 68-year-old female patient who was diagnosed with MDS in 2009 and subsequently started therapy with azacitidine who, similarly to our case, developed lesions on the upper limb at the administration site.[19] Doodnauth *et al.* also reported a case of a 76-year-old male patient diagnosed with MDS who developed Sweet syndrome after 7 days of azacitidine administration. Similarly to our case, the patient had neutropenia and the lesions appeared first at the site of azacitidine administration.[20]

Although our patient refused the biopsy, the diagnosis was supported by the lesions that appeared first at the site of azacitidine administration, which did not respond to antibiotic therapy but responded promptly to corticosteroid therapy.

Although rare, Sweet syndrome may also have extracutaneous manifestations affecting the central nervous system, lungs, kidneys, bones, muscles, eyes, spleen, and even intestines.[10] As far as treatment options are concerned, as mentioned above, corticosteroid therapy is the best first-line option. When corticosteroids are contraindicated, colchicine and dapsone are indicated as second-line therapy.[14]

CONCLUSIONS

Sweet syndrome is a rare condition that is difficult to diagnose because of the wide spectrum of differential diagnoses. We present the case of a patient in whom the diagnosis of Sweet syndrome and the initiation of corticosteroid therapy were delayed and resulted in worsening of the symptoms. Azacitidine administration is a rare cause of drug-induced Sweet syndrome. Perhaps the strongest evidence for the etiology of drug-induced Sweet syndrome is the temporal relationship between azacitidine administration and the appearance of Sweet syndrome lesions.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

DENTAL MEDICINE // PSYCHOLOGY

Pseudohalitosis – More than a Complicated Multidisciplinary Case

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ABSTRACT

Introduction: Halitophobia is also known as false halitosis or psychosomatic halitosis. This pseudo-pathology originates from the somatization of the compulsive idea that the patient has bad breath in the absence of oral pathology. **Case Presentation:** A patient addressed dental surgery complaining of a self-diagnosed halitosis. The dental consultation did not find any dental problem that could cause bad breath. She was referred to a general practitioner for further investigations to rule out a general condition. The investigations revealed a perfectly healthy person, without any chronic ailment that could cause bad breath. The patient refused to consult a psychologist or psychiatrist, considering that she does not have a mental health problem. **Conclusions:** Patients with a suspicion of psychogenic halitosis require psychiatric counseling, and dentists have to be prepared with an efficient strategy for the correct management of these patients.

Keywords: halitosis, oral pathology, psychiatric counseling

INTRODUCTION

Halitophobia is a type of pseudohalitosis or psychological halitosis in which the patient develops an obsession and continuous stress generated by the belief that they have bad breath. The fear that others might perceive their bad breath creates social anxiety. However, in these cases, bad breath cannot be subjectively or objectively confirmed by doctors.[1] Dentists often ignore the patients' persistent complaints of unpleasant odor, which is why many patients with psychosomatic halitosis fail to get adequate treatment for their condition. Proper management of the situation is essential, as some studies have highlighted a suicidal tendency in these patients.

CASE PRESENTATION

A patient presented to the dental office with a specific symptom, namely a presumed bad breath that has occurred as a result of SARS-CoV-2 infection. The patient had experienced a loss of smell and taste, which gradually reappeared about a month after the infection. Also, the patient was pre-menopausal, and the changes

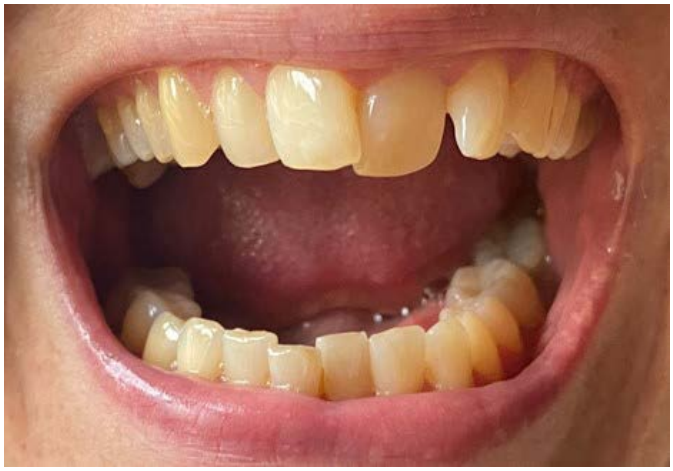

FIGURE 1. The patient's perfect oral hygiene

in taste and smell were also attributed to this. She underwent a specialist dental consultation, which did not reveal any dental disease. The patient had no carious processes or periodontal problems and did not wear a prosthesis. Oral hygiene indices revealed the presence of extraordinary oral hygiene, also confirmed by the anamnesis. The patient has developed an obsessive-compulsive tendency regarding oral hygiene; therefore, she brushed her teeth after every meal and constantly used mouthwash and oral sprays. She even reported using strong essential oils based on eucalyptol and peppermint. The patient was not a smoker.

To rule out any general condition that may cause bad breath, the patient was referred to a general practitioner for further investigations, none of which could confirm the presence of such a condition. She was then referred to a psychiatrist, which she categorically refused, considering that the doctors are not competent for her condition and stating that she is "not insane".

Her bad-smelling breath caused the patient social discomfort, avoiding speaking in public and deeply regretting the removal of the compulsory protective mask. The patient also avoided direct contact with people around her, and when talking to someone, she avoided eye contact and put her hand before her mouth in embarrassment. Her relationship with family members was also affected and tense.

The patient gave informed consent allowing the publication of her data, and the institution where the patient had been admitted, approved the publication of the case.

DISCUSSION

A correct diagnosis is very important for the proper management of halitosis. In a cross-sectional study on 407 patients with complaints of bad breath, halitosis could not be detected in 28% of cases, and more than 75% of the patients had their diagnosis established and received treatment from other medical specialties (gastroenterology in 33% and ENT in 14% of cases).[2]

In one study, 1,360 female students answered a questionnaire on psychological halitosis, olfactory reference syndrome, social anxiety, and preoccupation with odors caused by different body parts such as the mouth, armpits, and legs. The authors found that social anxiety may be a causal factor of subjective pathological halitosis and olfactory reference syndrome.[3] From a psychiatric perspective, halitophobia is considered a part of olfactory reference disorder, halitosis being one of its main symptoms.[4]

The classification of olfactory reference disorder as a mental disorder has been long debated. It Olfactory reference syndrome is a newly introduced condition in ICD-11 and is classified as an 'obsessive-compulsive or related disorder', the main symptom being the belief that the person emits a foul body odor.[5] DSM-IV and ICD-10 include concerns about emitting body odors in the description of somatic delusional disorder. However, these manifestations do not always become delusional. DSM-IV also mentions the fear of body odors as part of social phobia, as a symptom of the Asian cultural syndrome taijin kyofusho (fear of personal interaction).[6] Its variants are: shubo-kyofu, the phobia of a deformed body, and jikoshu-kyofu, the phobia of body odors, classified as specific obsessive-compulsive disorder. In DSM-5, it is classified as a disorder related to obsessive-compulsive disorder, and it is mentioned in connection with taijin kyofusho.[7]

CONCLUSIONS

As the perception of smells is subjective and is based on many etiological factors, the qualitative assessment of smells depends largely on our olfactory memory and individual personality traits. Therefore, identifying the real cause of halitosis sometimes remains difficult if the assessment is based on self-perception. The difficulty in finding a favorable treatment for halitophobia depends on whether the patient can be convinced to consult a psychologist or psychiatrist. A paraclinical examination using a portable device (halitosis detector), which objectively determines the number of volatile sulfur compounds, could be a decisive element in convincing the patient.

CONFLICT OF INTEREST

Nothing to declare.

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