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Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

The journal will try to provide the entire medical community with the perspective of the regional specifics of Central and Eastern European countries. The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

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REVIEW

GASTROENTEROLOGY // RHEUMATOLOGY

Etiopathogenic and Clinical Aspects in Inflammatory Bowel Disease – Literature Review

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory condition which encompasses Crohn's disease and ulcerative colitis. IBD does not only affect the gastrointestinal system, but also associates many extraintestinal complications that can affect almost any organ. A large number of patients may have these complications before or after the diagnosis of IBD. Early diagnosis and management of these complications involves a multidisciplinary team and contributes to decrease patient morbidity and mortality, but also to increase the quality of life. The purpose of this extensive literature review is to present systematically and comprehensively the latest data on the extraintestinal manifestations of IBD, and to draw clinicians' attention to the fact that this condition can have extradigestive manifestations that can be misleading and delay the diagnosis.

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, extraintestinal manifestations

INTRODUCTION

Inflammatory bowel disease (IBD) includes two clinical entities: Crohn's disease (CD) and ulcerative colitis (UC), both characterized by a chronic inflammation of the gastrointestinal tract, whose frequent signs and symptoms include abdominal pain, diarrhea and bloody stools. While UC is caused by a continuous inflammation of the colonic mucosa and submucosa, in CD the inflammation is full-thickness, discontinuous, and involves the entire digestive tract.[1] IBDs are commonly linked with the occurrence of extraintestinal manifestations (EIMs). These can affect almost any organ system, thus contributing to increased morbidity in patients with IBD.[2]

The pathophysiology of the disease has not been fully elucidated yet. The major determinants of IBD are genetic susceptibility, intestinal flora, lifestyle, and the immune system.[1] The pathogenesis of EIMs in IBD is unclear, but genetic factors and the immune system are thought to be involved. The immune response triggered by the gastrointestinal mucosa can affect extraintestinal areas due to common epitopes. Thus, translocated bacteria will trigger an adaptive immune response, unable to differentiate between bacterial or joint and skin epitopes.[3]

It has been shown that genetic susceptibility plays a major role. For instance, EIMs in CD occur more often in subjects that present HLA-A2, HLA-DP1, and HLA-DQW5 patterns. In UC, EIMs are more often present in subjects with HLA-DR103 haplotype. An increased probability for primary sclerosing cholangitis (PSC) in UC has been specifically associated with HLA-B8/D33.[2]

Short-chain fatty acids (SCFAs) create favorable conditions for resistance to pathogenic bacteria and prevent colitis, thus contributing to the maintenance of intestinal homeostasis. Lower levels of SCFA were found in patients with IBD and psoriatic arthritis.[4] Long-chain fatty acids (LCFAs) have a reciprocal relationship with IBD. Along with economic development, the morbidity of IBD has shown a significant increase, to a certain extent owed to eating habits (long-chain polyunsaturated omega-6/omega-3 fatty acids [PUFAs] and an abundance of saturated fats). Moreover, LCFAs are also involved in modulating intestinal lesions.[5]

1. ARTICULAR MANIFESTATIONS

Inflammatory arthropathies are the most common EIMs of subjects with IBD.[4] They are classified into axial and peripheral spondylarthritis, with a prevalence of 5–20% and 3–25%, respectively.[6] Peripheral arthropathies that occur as EIMs in patients with inflammatory disorders of the digestive tract are separated into two categories. Type I arthropathy, which is pauciarticular or oligoarticular, affects maximum 5 large articular areas and is characterized by an acute, asymmetrical, and migratory pattern. It is associated with HLA-B27, HLA-B35, and HLA-DR103 haplotypes. The symptoms persist for less than 10 weeks, are self-limiting, do not cause permanent destruction of the joint, and are correlated with the intestinal activity.[7] Type II arthropathy has a polyarticular pattern and may involve 5 or more small joints. The symptoms can persist for months or years and are independent of the disease course. The second type is associated with HLA-B44.[7]

Axial arthropathies are independent of the disease activity. The most common symptoms are back pain and morning stiffness, and may be present before the intestinal symptoms of IBD.[7]

Patients with IBD may experience decreased bone mineral density due to changes in absorption caused by multiple factors: intestinal resections, mineral malabsorption and vitamin D deficiency, corticosteroid treatment, and microbiota interaction. Osteoporosis is characterized by decreased bone mass and deterioration of bone microarchitecture, thus causing an increase in bone fragility and in the risk of fractures.[8] Alendronate and risedronate are the most widely used therapies in the prevention of vertebral and non-vertebral fractures, with long established efficacy.[8]

2. MUCOSAL SKIN MANIFESTATIONS

Mucocutaneous manifestations in IBD are common and cover a wide spectrum of manifestations that range from mild to severe and even debilitating.[9] The prevalence of these lesions is 10–15%. The most frequent mucocutaneous clinical manifestations in IBD are erythema nodosum and pyoderma gangrenosum. Rare manifestations are psoriasis and Sweet's syndrome.[7]

Erythema nodosum is the most common cutaneous manifestation of IBD, with a prevalence of 3–10% in patients with UC and 4–15% in patients with CD. It occurs more frequently in women and in patients with HLA-B27 haplotype. Erythema nodosum is characterized by the presence of symmetrical, erythematous, warm, painful, non-ulcerative nodules, with dimensions between 1–5 cm, located mainly on the extensor surfaces of the lower limbs.[10]

Pyoderma gangrenosum is a severe cutaneous manifestation, with a prevalence of 1–2% in patients with IBD, being more frequently associated with UC. This condition can be expressed before, during, or after the onset of IBD, but it can be independent also. More frequently, it affects women and patients with a family history of UC.[10] Although many forms of manifestation have been described (ulcerative, bullous, pustular, vegetative, drug-induced, postoperative, and peristomal), the most common types in IBD are ulcerative and pustular. The initial lesion presents papules, pustules, or nodules with violaceous, irregular edges, which subsequently evolve towards painful ulceration.[10]

Sweet's syndrome is an acute febrile neutrophilic dermatosis, rarely associated with IBD. The prevalence is higher in patients with CD than in those with UC and among women aged 30–50 years.[9] This syndrome is char-

acterized by the presence of papules, nodules, and erythematous plaques with a tendency to confluence, located especially on the face, neck, and upper limbs.[10] Sweet's syndrome can affect not only the skin but also other organs such as the lungs, muscles, joints, liver, kidneys, and eyes.[9]

3. ORAL MANIFESTATIONS

Oral manifestations in IBD are specific or nonspecific and may precede or coincide with the diagnosis. The most common is aphthous stomatitis with a prevalence between 0.7% and 20%. It is characterized by the presence of small, painful ulcers surrounded by an erythematous halo. In patients with IBD, the lesions may be secondary to iron, zinc, or vitamin B12 deficiency, or IBD therapy.[11] The oral manifestation secondary to mesalazine and sulfasalazine treatment is oral lichen planus,[12] and correlated with the administration of infliximab are oral ulcerations.[11]

4. EYE MANIFESTATIONS

About 2–5% of patients with IBD have ocular symptoms. They arise more often in subjects with CD (3.5–6%) compared to UC (1.6–4.6%)[7] and are represented by episcleritis, scleritis, uveitis, and conjunctivitis.[2] Besides the ocular manifestations due to IBD, ocular complications secondary to specific therapy can also be observed. Corticosteroids can cause cataract and open-angle glaucoma. Cyclosporine can cause ophthalmoplegia, nystagmus, and optic neuropathy.[7]

Episcleritis is the most frequent ocular manifestation and consists in a benign inflammatory reaction in the sclera. It may present with moderate discomfort, erythema in one or both eyes, and diffuse or localized episcleral edema. Compared to other ocular manifestations, episcleritis may be associated with IBD activity.[13]

Scleritis is an inflammation of the sclera that causes eye pain, irradiated towards the face and scalp. Specific for this pathology is the aggravation of symptoms during the night, associating ocular hyperemia and visual loss.[13]

Uveitis is defined as an inflammation of the uveal tract and is currently the third leading cause of irreversible blindness in developed countries. In patients with IBD, it has an insidious onset, is long-lasting, bilateral, and does not correlate with disease activity.[13]

5. HEPATOBILIARY MANIFESTATIONS

The hepatic involvement of IBD most often includes PSC. Uncommon hepatobiliary alterations linked with IBD are autoimmune hepatitis/PSC overlap syndrome: IgG-associated cholangiopathy, primary biliary cholangitis, portal vein thrombosis and liver abscess, as well as hepatic amyloidosis, granulomatous hepatitis, and cholelithiasis. The most common liver disease in individuals with IBD that is not correlated with intestinal activity is non-alcoholic fatty liver disease (NAFLD).[14]

The prevalence of PSC varies between 2.4% and 7.5% in those with UC and is 3.4% in patients with CD.[15] PSC may lead to multiple hepatic and biliary complications including cirrhosis, liver insufficiency, and portal hypertension. Patients with PSC have a high risk of cholangiocarcinoma, and the association between PSC and IBD increases the risk of colorectal cancer. PSC affects the activity and localization of IBD. It is associated with a more extensive form of UC (pancolitis), but with lower rates of activity and colectomy. In patients with CD and PSC, the most common forms are colitis and ileocolitis.[16]

The treatment used in IBD can cause liver toxicity. Methotrexate and thiopurine have the highest risk of hepatotoxicity. Aminosalicylates can rarely cause hepatotoxicity, whereas cases of granulomatous hepatitis and fulminant hepatitis have been reported in the literature.[16]

Since during immunosuppressive treatment reactivation of hepatitis B virus (HBV) is possible, it is necessary to screen patients and vaccinate the seronegative (HBsAg and anti-HBc negative).[16]

6. PANCREATIC MANIFESTATIONS

Pancreatic manifestations in subjects with IBD include asymptomatic growth of pancreatic enzymes, acute or chronic pancreatitis, exocrine pancreatic failure, or malignancy. Acute pancreatitis can be favored by gallstones, drugs (mesalazine, thiopurine), duodenal papillary lesions, endoscopic procedural accidents, PSC, and autoimmune pancreatitis.[17]

A recent Danish meta-analysis showed a three-fold risk of developing acute pancreatitis in patients with CD and a two-fold risk in patients with UC.[18]

The link between IBD and chronic pancreatitis, exocrine pancreatic insufficiency, and pancreatic cancer is not very clear yet, and additional studies are needed.[17]

7. PULMONARY MANIFESTATIONS

Pulmonary manifestations occur rarely in patients with IBD.[7] The airways and the gastrointestinal tract have common embryonic origins and a similar structure. The lymphoid tissue present in the mucosa of both organs plays a key

role. Thus, the mechanisms involved in the development of inflammation are: migration of activated lymphocytes from the gastrointestinal tract to the respiratory tract, the presence of common antigens (bacteria, digestive enzymes) due to loss of intestinal epithelial barrier function, and the presence of antibodies and immune complexes.[19] Pulmonary manifestations involve the small and large airways, as well as the parenchyma. Extraintestinal complications are drug-induced lung diseases.[7] Numerous case reports have concluded that respiratory symptoms can be triggered during both periods of IBD activity and remission.[19]

The most common form of EIMs affects the large airways and is more frequently associated with UC. Bronchial inflammation and suppuration are the most common manifestations of lung disease in IBD and include chronic bronchitis and bronchiectasis. The latter is the most commonly reported, with a prevalence of 66% in patients with large airway involvement.[20]

Lung parenchymal disease is associated with IBD less frequently. The age of onset varies, has a slight female predominance, and is frequently associated with UC. Bronchiolitis obliterans organizing pneumonia (BOOP) is the most common parenchymal manifestation. BOOP can be caused by inhalation or medication injuries and has an acute or subacute onset with fever, cough, dyspnea, and pleuritic chest pain.[21]

The treatment of patients with IBD can cause lung complications. The use of azathioprine (AZA) and 6-mercaptopurine (6-MP) may cause interstitial pneumonia, BOOP, chronic fibrosis/pneumonitis, and pulmonary edema. Long-term use of sulfasalazine and mesalamine may cause eosinophilic pleuritis, eosinophilic pneumonia, and BOOP. Methotrexate may cause the following lung side effects: interstitial pneumonitis, granuloma formation, and bronchiolitis. Biological anti-TNF-α therapy (infliximab, adalimumab, certolizumab) may also cause side effects, requiring close monitoring of therapy. As a result of the suppression of T cell-mediated immunity, various associated opportunistic infections have been observed, the most common being tuberculosis. Other lung infections associated with biological therapy, especially in the elderly, are: *Pneumocystis carinii* pneumonia, coccidiomycosis, histoplasmosis, aspergillosis, and actinomycosis.[20]

8. CARDIOVASCULAR MANIFESTATIONS

Cardiovascular changes related to IBD include: pericarditis, myocarditis, venous and arterial thromboembolism, heart failure, arrhythmias and conduction disorders, endocarditis, valvulopathy, and Takayasu's arteritis.[22]

The incidence of cardiovascular manifestations is slightly increased compared to the general population. This is supported by a recent cohort study which showed that the prevalence of traditional cardiovascular risk factors is quite low in patients with IBD.[23] The most common cardiovascular EIM is represented by pericarditis, with a prevalence of 0.19% in patients with CD and 0.23% in patients with UC.[22,24]

The risk of arterial thromboembolic events is increased in patients with IBD, with a similar prevalence in patients with CD and UC. The most common arterial thromboembolic events are acute myocardial infarction, stroke, and mesenteric infarction, with an incidence that is 1.2-, 1.2-, and 3.5-fold higher, respectively, compared to the general population. IBD exacerbations are favorable factors for the occurrence of these events.[22]

Patients with IBD have a two-fold risk of heart failure compared to the control group. When these two conditions coexist, the risk of using systemic corticosteroids is 2.5 times higher.[22] The incidence of atrial fibrillation in patients with IBD is 11.3%, and the arrhythmic risk increases two-fold during IBD exacerbations compared to the general population.

The association between IBD and endocarditis, mitral and aortic regurgitation and Takayasu's arteritis is very rare.[22]

9. ANEMIA

The prevalence of anemia in patients with IBD varies between 6% and 74%. This very wide variation of prevalence is due to the evaluation criteria used for defining anemia, the type of population investigated (hospitalized /discharged patients, type of IBD, age of patients), but also the evaluation time (at the time of diagnosis, during the disease).[25]

The etiopathogenesis of anemia is multifactorial, but in patients with IBD the most common types of anemia are those due to iron deficiency caused by chronic blood loss, decreased iron absorption, or malnutrition. Other causes that may contribute are vitamin B12 and folate deficiency, as well as the toxic effect of drugs.[26] Anemia can increase the rate of hospitalizations in patients with IBD and has a negative impact on both quality of life, and cognitive function and work capacity.[27]

10. IMMUNE THROMBOCYTOPENIC PURPURA

The presence of immune thrombocytopenic purpura (ITP) in patients with IBD has been described in a limited number of cases.[28] Researchers support the theory of anti-

genic mimicry between platelet surface and luminal antigens, thus creating a common immune-mediated pathway to mucosal inflammation and platelet destruction. Studies have shown increased levels of T-helper 1 and CD4 cells.[29]

11. RENAL AND GENITOURINARY MANIFESTATIONS

Patients with IBD have a prevalence of renal impairment of 4–23%.[7] Renal manifestations include nephrolithiasis, glomerulonephritis, tubulointerstitial nephritis, and amyloidosis.[30] The most common form of glomerulopathy in patients with IBD is IgA nephropathy, which is associated with HLA-DR1. Tubulointerstitial nephritis may be a drug-induced complication of IBD caused by the administration of 5-aminosalicylic acid and sulfasalazine.[7] Nephrolithiasis affects 5–15% of patients with IBD, predominantly those with CD and ileo-colonic involvement. The most common stones are those of calcium oxalate (by malabsorption of bile acids) and those of uric acid (by decreasing urinary pH and urinary volumes).[7]

A recent cohort study (SIBDCS) on 2,323 patients showed that intestinal surgery, especially ileal/ileo-colonic surgery, may increase the incidence of kidney stones.[31]

A recent study on genital manifestations showed that the prevalence of cervical dysplasia and HPV 16/18 infection was significantly higher than in the control group.[32]

12. DEPRESSION AND ANXIETY DISORDERS

Anxiety disorders and depression are more common in patients with IBD compared to the general population. This relationship has not been fully elucidated, but the suggested mechanisms include activation of the inflammatory response in the brain, compromised integrity of the blood-brain barrier, and the impact of the intestinal microbiota.[33] A Canadian study on 6,000 patients with IBD showed that the prevalence and incidence of depression, anxiety, and bipolar disorders were significantly higher compared to the general population.[33]

A recent analysis of non-pharmacological therapy that included 10 studies showed that cognitive behavioral therapy, as well as attention-based and solution-based therapy significantly contributed to the reduction of anxiety and depression in adults compared to control groups.[34]

13. NEUROLOGICAL MANIFESTATIONS

The most common neurological manifestations in patients with IBD are peripheral neuropathies, unrelated to intestinal activity. In patients with CD and ileocecal resection, a typical neurological complication is found, namely peripheral polyneuropathy due to vitamin B12 deficiency.[35]

Focal intracerebral lesions of the white matter were detected in 42% of patients with CD and in 46% of patients with UC. Recurrent facial paralysis associated with Melkerssson-Rosenthal syndrome has been specifically observed in some patients with CD.[7]

Anti-TNF-α therapy is associated with Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, while metronidazole and sulfasalazine may induce peripheral neuropathy.[36]

CONCLUSIONS

In our extensive analysis we highlighted that extraintestinal manifestations of IBD are very frequent, can affect almost any organ system, and have the potential to become more debilitating than the intestinal disease itself. We therefore draw attention to the importance of proper recognition and treatment of extraintestinal manifestations of IBD that will help reduce patient morbidity and mortality, as well as improve quality of life.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Zhao J, Lu Q, Liu Y, et al. Th17 Cells in Inflammatory Bowel Disease: Cytokines, Plasticity, and Therapies. *Journal of Immunology Research*. 2021;1-14.
2. Jang HJ, Kang B, Choe BH. The difference in extraintestinal manifestations of inflammatory bowel disease for children and adults. *Transl Pediatr*. 2019;8:4-15.
3. Martinez-Fierro ML, Garza-Veloz I, Rocha-Pizaña MR, et al. Serum cytokine, chemokine, and growth factor profiles and their modulation in inflammatory bowel disease. *Medicine (Baltimore)*. 2019;98:e17208.
4. Kim JM, Cheon JH. Pathogenesis and clinical perspectives of extraintestinal manifestations in inflammatory bowel diseases. *Intest Res*. 2020;18:249-264.
5. Ma C, Vasu R, Zhang H. The Role of Long-Chain Fatty Acids in Inflammatory Bowel Disease. *Mediators Inflamm*. 2019;2019: 8495913.
6. Malaty HM, Lo GH, Hou JK. Characterization and prevalence of spondyloarthritis and peripheral arthritis among patients with inflammatory bowel disease. *Clin Exp Gastroenterol*. 2017;10:259-263.
7. Chams S, Badran R, Sayegh SE, Chams N, Shams A, Hajj Hussein I. Inflammatory bowel disease: Looking beyond the tract. *Int J Immunopathol Pharmacol*. 2019;33:1-18.
8. Kotze LM, Costa CT, Cavassani MF, Nisihara RM. Alert for bone alterations and low serum concentrations of vitamin D in patients with intestinal inflammatory disease. *Rev Assoc Med Bras*. 2017;63:13-17.
9. Ungureanu L, Cosgarea R, Alexandru Badea M, et al. Cutaneous manifestations in inflammatory bowel disease (Review). *Exp Ther Med*. 2020;20:31-37.
10. Antonelli E, Bassotti G, Tramontana M, et al. Dermatological Manifestations in Inflammatory Bowel Diseases. *J Clin Med*. 2021;10;1-16.
11. Lauritano D, Boccalari E, Di Stasio D, et al. Prevalence of Oral Lesions and Correlation with Intestinal Symptoms of Inflammatory Bowel Disease: A Systematic Review. *Diagnostics (Basel)*. 2019;9:1-16.

12. Kumar KM, Nachiammai N, Madhushankari GS. Association of oral manifestations in ulcerative colitis: A pilot study. *J Oral Maxillofac Pathol*. 2018;22:199-203.
13. Troncoso LL, Biancardi AL, de Moraes HV Jr, Zaltman C. Ophthalmic manifestations in patients with inflammatory bowel disease: a review. *World J Gastroenterol*. 2017;23:5836-5848.
14. Silva J, Brito BS, de N. Silva IN, et al. Frequency of Hepatobiliary Manifestations and Concomitant Liver Disease in Inflammatory Bowel Disease Patients. *Biomed Res Int*. 2019;2019:7604939.
15. de Vries AB, Janse M, Blokzijl H, Weersma RK. Distinctive inflammatory bowel disease phenotype in primary sclerosing cholangitis. *World J Gastroenterol*. 2015;21:1956-1971.
16. Fousekis FS, Theopistos VI, Katsanos KH, et al. Hepatobiliary Manifestations and Complications in Inflammatory Bowel Disease: A Review. *Gastroenterol Res*. 2018;11:83-94.
17. Iida T, Wagatsuma K, Hirayama D, Yokoyama Y, Nakase H. The Etiology of Pancreatic Manifestations in Patients with Inflammatory Bowel Disease. *J Clin Med*. 2019;8:916.
18. Fousekis FS, Theopistos VI, Katsanos KH, Christodoulou DK. Pancreatic Involvement in Inflammatory Bowel Disease: A Review. *J Clin Med Res*. 2018;10:743-751.
19. Kacprzak A, Szturmowicz M, Kus J. Respiratory system involvement in inflammatory bowel diseases. *Adv Respir Med*. 2017;85:161-168.
20. Ji XQ, Wang LX, Lu DG. Pulmonary manifestations of inflammatory bowel disease. *World J Gastroenterol*. 2014;20:13501-13511.
21. Xu L, Xiao W, Ma D, Zhou S, Zhang Q. Ulcerative colitis combined with acute interstitial lung disease and airway disease: A case report and literature review. *Exp Ther Med*. 2014;8:1229-1236.
22. Bunu DM, Timofte CE, Ciocoiu M, et al. Cardiovascular Manifestations of Inflammatory Bowel Disease: Pathogenesis, Diagnosis, and Preventive Strategies. *Gastroenterol Res Pract*. 2019;2019:3012509.
23. Harbord M, Annese V, Vavricka SR, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis*. 2016;10:239-254.
24. Mitchell NE, Harrison N, Junga Z, Singla M. Heart Under Attack: Cardiac Manifestations of Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2018;24:2322-2326.
25. Ali SA, Abbasi Z, Shahid B, et al. The prevalence, characteristics, and determinants of anaemia in newly diagnosed patients with inflammatory bowel disease. *Gastroenterology Rev*. 2019;14:39-47.
26. Tulewicz-Marti E, Moniuszko A, Rydzewska G. Management of anemia in inflammatory bowel disease: a challenge in everyday clinical practice. *Gastroenterol Rev*. 2017;12:239-243.
27. Nemes RM, Pop CS, Calagiu D, et al. Anemia in inflammatory bowel disease more than an extraintestinal complication. *Rev Med Chir*. 2016;120:34-39.
28. Epistola R, Do T, Vankina R, et al. Immune thrombocytopenic purpura (ITP) as an uncommon extraintestinal complication of Crohn's disease: case vignette and systematic literature review. *Case Rep Hematol*. 2020;2020:4785759.
29. Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of Iron Deficiency Anemia. *Gastroenterol Hepatol (N Y)*. 2015;11:241-250.
30. Fagagnini S, Heinrich H, Rossel JB, et al. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. *PLoS ONE*. 2017;12:e0185193.
31. Pittet V, Juillerat P, Mottet C, et al. Cohort Profile: The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *Int J Epidemiol*. 2009;38:922-931.
32. Li M, Yang QF, Cao Q, et al. High-risk human papilloma virus infection and cervical neoplasm in female inflammatory bowel disease patients: a cross-sectional study. *Gastroenterol Rep (Oxf)*. 2019;7:338-344.
33. Kuźnicki P, Kempiński R, Neubauer K. The emerging role of mood disorders in inflammatory bowel diseases. *Adv Clin Exp Med*. 2020;29:1505-1510.
34. Davis SP, Bolin LP, Crane PB, Crandell J. Non-pharmacological Interventions for Anxiety and Depression in Adults With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Front Psychol*. 2020;11:538741.
35. Singh S, Kumar N, Loftus EV Jr, Kane SV. Neurologic complications in patients with inflammatory bowel disease: increasing relevance in the era of biologics. *Inflamm Bowel Dis*. 2013;19:864-872.
36. Ott C, Schölmerich J. Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol*. 2013;10:585-595.

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ORIGINAL RESEARCH

DIABETES, NUTRITION AND METABOLIC DISEASES // PSYCHIATRY

Factors Associated with Diabetes-Related Distress in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: The aim of this study was to identify factors associated with diabetes-related distress (DRD) in adult patients with type 2 diabetes mellitus (T2DM). **Material and Methods:** This was an analysis of data previously obtained from two cross-sectional studies, in which medical charts review and direct interviews were employed to obtain medical and demographic data. Vital status assessment and anthropometric measurements were performed. The patients filled out specific questionnaires for DRD (DDS-17), symptoms of depression (PHQ-9), and of anxiety (GAD-7). A clinical meaningful threshold for DRD was set at ≥2.0 points. Symptoms of depression and anxiety, number of chronic complications, therapy for T2DM, anthropometric and cardio-metabolic parameters, as well as demographic, socio-economic data, and lifestyle habits were evaluated as factors possibly associated with DRD by univariate and multiple regression analyses. **Results:** A total of 271 patients with T2DM were included in this analysis, of whom 25.1% presented a DDS-17 score ≥2 points (and 9.96% a DDS-17 score ≥3). Subjects with a DDS-17 score ≥2 had higher HbA1c levels ($p = 0.018$), PHQ-9 and GAD-7 scores ($p < 0.0001$ for both). The multiple regression model indicated that anxiety ($p = 0.026$), depression ($p = 0.001$), and ethnicity ($p = 0.002$) were significantly correlated with DRD ($p < 0.0001$). With regards to subscales, the HbA1c ($p = 0.005$) and PHQ-9 score ($p < 0.0001$) were significantly associated with emotional burden, ethnicity ($p = 0.001$) and depression ($p = 0.004$) with regimen-related distress, whereas ethnicity ($p = 0.010$) and GAD-7 score ($p = 0.012$) with interpersonal distress. **Conclusions:** Psychosocial factors like depression, anxiety, or ethnicity significantly contribute to DRD in patients with T2DM, and worse glycemic control is associated with emotional burden.

Keywords: type 2 diabetes mellitus, diabetes-related distress, depression, anxiety

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that requires lifelong, comprehensive care, and is frequently associated with neuropsychological comorbidities, such as depression, anxiety, or cognitive impairment,

conditions that may affect the metabolic control, diabetes self-care behaviors including medication adherence, and quality of life.[1–5]

In addition, it is apparent that a high proportion of T2DM patients also present diabetes-related distress (DRD), defined as psychological reactions or emotions that they might experience. These psychological reactions are basically concerns related to disease management, perception of support, access to quality healthcare, or emotional burden.[6] A systematic review and meta-analysis of 55 studies (n = 36,998 subjects) indicated that 36% of individuals with T2DM suffer from DRD (but with very large variations, ranging from to about 10% to over 60%).[7–9] The difference may be due to patient selection, geographical area/ethnicity, method of assessment and interpretation, or the presence of comorbid conditions, such as coexistence of depression, which increases the prevalence of DRD.[7]

Female gender and depression were the only factors identified in the meta-analysis of Perrin *et al*. as being associated with DRD, but a plethora of other factors emerged from the literature such as age, body mass index (BMI), glycemic control, duration of diabetes, lifestyle habits, treatment regimens, level of education etc.[7,10–16]

DRD has important health-related consequences such as worse glycemic outcomes, poorer medication adherence and diabetes self-care, and poorer quality of life.[5,17] A recent study reported that in patients with T2DM, depressive symptoms were associated with lower self-management behavior and higher glycated hemoglobin (HbA1c), while DRD was associated with higher HbA1c, suggesting that patients with both depression and DRD might have worse outcomes.[18]

During recent years, there has been an increasing interest regarding the association between T2DM and DRD, yet currently there are scarce data regarding DRD in patients with T2DM from Romania.

The aim of this study was to identify factors that have a significant impact on DRD in adult patients with T2DM, by exploring a number of demographic, socio-economic, and lifestyle factors, cardio-metabolic parameters, type of treatment, and chronic complications.

MATERIAL AND METHODS

This was a post-hoc analysis of data obtained in two cross-sectional studies that screened adult patients with T2DM for symptoms of depression and anxiety, and for DRD using specific questionnaires, in 2015, and between 2018 and 2019, respectively. Each of the studies were approved by the ethics committees of the Emergency County Clinical Hospital of Târgu Mureş and of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureş, and patients signed an informed consent before participating. Patients were recruited from two specialty-care settings, the Diabetes, Nutrition and Metabolic Diseases Outpatient Unit of the Emergency County Clinical Hospital in Târgu Mureş (one specialist physician) and from the Puls Medical Center in Târgu Mureș (two specialist physicians).

The two studies had similar inclusion and exclusion criteria and design.[1] The included patients were aged >18 years, diagnosed with T2DM according to the American Diabetes Association criteria.[19] Main exclusion criteria were patients with type 1 diabetes mellitus, secondary diabetes mellitus, and gestational diabetes mellitus, severe psychiatric disorders, or unable to read Romanian language.

Both studies collected demographic and socio-economic data obtained from the medical charts and from a direct interview (age, gender, residency, education level, economic level, ethnicity, occupation, marital status), medical history (diabetes duration, micro- and macrovascular complications of diabetes, medication for T2DM and other comorbidities), information regarding lifestyle (level of physical exercise, smoking, alcohol, and coffee intake). Additionally, basic anthropometric parameters (weight, height, abdominal circumference), as well as heart rate and blood pressure measurements were performed, all by standard procedures. The BMI was calculated as weight (kg)/height^2 (m^2).

In the first study, 145 of the 216 included T2DM patients had laboratory testing performed by drawing blood during the study, while for the remaining, the laboratory information was collected from their medical charts (and included in this analysis only if they were available in the last three months).[1] For patients enrolled in the second study (2018–2019), laboratory tests (HbA1c, fasting blood glucose, and basic biochemistry) were collected from medical charts (if results from the last three months were available).

The subjects completed three questionnaires translated to Romanian. DRD was evaluated using the 17-item Diabetes Distress Screening Scale (DDS-17) questionnaire. DDS-17 is one of the two well-accepted tools for evaluation of DRD. It consists of 17 questions, each having assigned between 1 to 6 points. A score ≥2 points for DRD was considered positive (and interpreted as mild DRD), while a score ≥3 points was considered as significant DRD.[13,20,21] DDS-17 consists of 4 subscales, each evaluating a different aspect: emotional burden (EB), physician-related distress (PD), regimen-related distress (RD), and interpersonal distress (ID). The interpretation of each subscale was performed in a similar manner as for general

score. The symptoms of depression and anxiety were assessed by the Patient Health Questionnaires-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) questionnaires, respectively. For the PHQ-9 questionnaire, a score of ≥5 points indicated mild depression, ≥10 points moderate depression, and ≥15 points severe depression.1,22 For the GAD-7 questionnaire, a score of ≥5 points indicated mild anxiety, ≥10 points moderate anxiety, and ≥15 points severe anxiety.[1,23]

Statistical analysis

Continuous variables with a normal distribution were presented as mean (standard deviation [SD]), while those non-normally distributed as median (min-max), and categorical variables as frequency (%). The Kolmogorov-Smirnov test was used to determine whether the data had a normal distribution. For categorical variables, Fisher's exact test was used, and the odds ratios (OR) were calculated. Student's t test or the Mann-Whitney test was used to compare the differences between groups, and the bivariate relationships between variables were evaluated by Spearman's test (correlation coefficients presented as r (95% CI [confidence interval]). In order to identify independent associations between DRD and each domain with relevant parameters, we have performed a hierarchical multiple regression model, separately for the total DRD score and for each subscale. Model 1 included demographic, socioeconomic, and medical variables that were identified in the bivariate analysis as being significantly associated with DRD. Model 2 additionally included PHQ-9 and GAD-7 scores, to fully adjust for depression and anxiety. We have chosen these two conditions, as data in the literature and our previous partial data indicated them as being significant for DRD.

All tests were two-tailed, and the statistical significance was set at $p < 0.05$. Statistical analysis was performed using GraphPad InStat3.

RESULTS

From the two studies, a total of 316 patients with T2DM were included in this analysis. Duplicate examinations and patients lacking laboratory data in the last three months were excluded. In the end, data from 271 patients were analyzed. Table 1 presents the demographic, clinical, and metabolic characteristics of patients with T2DM with and without DRD (a DDS-17 score of ≥2 points).

T2DM patients with clinically meaningful DRD had a better economic level, were rather of Romanian ethnicity, and had higher GAD-7 and PHQ-9 scores, as well as higher HbA1c values (Table 1). No other statistically significant differences were noted between the two groups.

In this pooled population, 25.1% of T2DM patients presented a DDS-17 score ≥2 (and 9.96% had a score ≥3). Not only the PHQ-9 and the GAD-7 scores were higher in the DRD group (Table 1), but more T2DM patients with DRD presented more severe degrees of both anxiety and depression (Figure 1). Also, significantly more patients with both PHQ-9 and GAD-7 scores ≥10 points had a DDS-17 score ≥2 points compared with those with negative scores (<5 points) (OR 8.91, 95% CI 3.77 to 21.08, $p < 0.0001$). In addition, T2DM patients that presented both a PHQ-9 and a GAD-7 score ≥10 points (moderate/severe depression and anxiety, respectively) had a significantly higher DDS-17 score than those with both scores <5 points (negative for depression and anxiety) (2.11 [min: 1.06; max: 4.53] vs. 1.24 [min: 1.0; max: 3.76], $p < 0.0001$).

With regards to the DRD domains, in this pooled population a higher prevalence was observed for EB (38.74%) and RD (40.59%), while PD was noted in 8.48%, and ID in 19.18% of the T2DM patients. Moreover, T2DM patients with both moderate/severe depression and anxiety had a significantly higher score for EB (2.6 [min: 1.0; max: 6.0] vs. 1.2 [min: 1.0; max: 4.6], $p < 0.0001$), RD (2.3 [min: 1.0; max: 5.2] vs. 1.4 [min: 1.0; max: 4.0], $p < 0.0001$) and ID (1.33 [min: 1.0; max: 6.0] vs. 1.0 [min: 1.0; max: 5.67], $p = 0.002$) compared with patients with both negative scores.

The bivariate analysis indicated significant positive correlations between the DDS-17 score and BMI, heart rate, HbA1c, and fasting blood glucose, and negative correlations with age, ethnicity, and occupation (Table 2). The EB scores were negatively correlated with age and occupation, and positively with HbA1c, the PD scores were inversely correlated with ethnicity and positively correlated with heart rate, while the RD scores were positively correlated with HbA1c levels and fasting blood glucose, and negatively with age and occupation. In addition, anxiety and depression scores were positively associated with the total DDS-17 score and with all four subscales. For the rest of the parameters (presented in Table 1), there were no statistically significant correlations with none of the scores (data not shown). The strongest correlations of GAD-7 and PHQ-9 scores were observed with EB and with overall DRD, while all other correlations were weaker (Table 2).

In order to evaluate which of the variables have an independent, significant impact on DRD, we have further performed a stepwise multivariate regression analysis for the total DDS-17 score and each domain separately, by using variables that showed a significant correlation in

TABLE 1. Demographic, clinical and metabolic characteristics of patients with T2DM without and with DRD

	DDS-17 score <2 (n = 203)	DDS-17 score ≥2 (n = 68)	p value
Demographic and socioeconomic data			
Age, years (min; max)	64.0 (39.0; 88.0)	60.5 (44.0; 78.0)	0.158
Gender, F/M, n (%)	118 (58.1)/85 (41.9)	47 (69.1)/21 (30.9)	0.116
Residency, R/U, n (%)	47 (23.2)/156 (76.8)	12 (17.6)/56 (82.4)	0.398
Education, <12/≥12 years*, n (%)	120 (59.1)/83 (40.9)	25 (36.8)/43 (63.2)	0.570
Economic level, low/moderate/high&, n (%)	10 (4.9)/156 (76.9)/37 (18.2)	4 (5.9)/50 (73.5)/14 (20.6)	0.045
Ethnicity, R/H/Rr, n (%)	120 (59.1)/79 (38.9)/4 (2.0)	53 (77.9)/13 (19.2)/2 (2.9)	0.016
Occupation, A/R or UE, n (%)	41 (20.2)/162 (79.8)	18 (26.5)/50 (73.5)	0.309
Marital status, M/S, n (%)	149 (73.4)/54 (26.6)	49 (72.1)/19 (27.9)	0.874
Lifestyle data			
Level of physical exercise&, low/moderate/high, n (%)	54 (26.6)/127 (62.6)/22 (10.8)	19 (27.9)/46 (67.6)/3 (1.5)	0.334
Smoking status, Sm/NSm, n (%)	29 (14.3)/174 (85.7)	9 (13.2)/59 (86.8)	1.000
Alcohol intake&, R/Oa, n (%)	148 (72.9)/55 (27.1)	50 (73.5)/18 (26.5)	1.000
Coffee intake&, Oc/Hb, n (%)	41 (20.2)/162 (79.8)	17 (25.0)/51 (75.0)	0.398
Medical data			
Diabetes duration, years (min; max)	4.0 (0; 26.0)	4.5 (0.5–19.0)	0.924
BMI, kg/m^2 (min; max)	30.8 (21.1; 51.5)	31.5 (23.8–62.5)	0.078
Waist circumference, cm (min; max)	106.0 (76.5; 149.0)	108.5 (90.0–108.5)	0.514
Systolic blood pressure, mmHg (min; max)	139.2 (120; 158.4)	136.4 (116.2; 156.6)	0.302
Diastolic blood pressure, mmHg (min; max)	80.0 (45.0; 131.0)	80.0 (55.0–97.5)	0.279
Heart rate, b/min (min; max)	75.0 (54.0; 152.0)	78.0 (56.0–113.0)	0.100
HbA1c, % (min; max)	6.45 (4.2; 12.4)	6.65 (5.2–12.3)	0.018
Fasting blood glucose, mg/dL (min; max)	127 (78; 254)	133 (87–332)	0.191
Total cholesterol, mg/dL (min; max)	183.3 (95.7; 326.0)	188.5 (64.0–306.7)	0.601
Triglycerides, mg/dL (min; max)	141.1 (47.4; 856.0)	151.7 (40.0–765.8)	0.162
Type of T2DM medication, NI/I, n (%)	150 (73.9)/53 (26.1)	52 (76.5)/16 (23.5)	0.749
Microvascular complications, no./person (min; max)	0.0 (0.0; 3.0)	0.0 (0.0–2.0)	0.146
Macrovascular complications, no./person (min; max)	0.0 (0.0; 3.0)	1.0 (0.0–2.0)	0.207
Total chronic diabetes complications, no./person (min; max)	1.0 (0.0; 5.0)	1.0 (0.0–4.0)	0.924
Depression and anxiety data			
PHQ-9 score, mean (min; max)	4 (0; 27)	9 (0–25)	<0.0001
GAD-7 score, mean (min; max)	3 (0; 21)	7.5 (0–21)	<0.0001

F – female; M – male; nr – number; R – rural; U – urban; *years of formal education; &self-declared; R – Romanian; H – Hungarian; Rr – Rroma; A – active; R – retired; UE – unemployed; M – married (or living with a partner); S – single (not married/widowed/divorced); Sm – smoker; NSm – non-smoker/ex-smoker; R – regular (daily/weekly); Oa – occasionally (< one time/week); Oc – occasionally (weekly or more rare); Hb – habitual (at least one daily); BMI – body mass index; b/min – beats/minute; HbA1c – glycated hemoglobin; NI – non-injectable; I – injectable

the bivariate analysis (Table 3). The first model included demographic, socio-economic, and medical parameters (age, fasting blood glucose, HbA1c, heart rate, BMI, ethnicity, and occupation), and in the second model GAD-7 and PHQ-9 scores were added.

In model 1, the BMI was positively (but weakly) correlated with the total DDS-17 score (p = 0.0387), EB (p = 0.028), and RD (p = 0.003), while HbA1c was correlated with EB (p = 0.001) (Table 3). Ethnicity significantly associated with the overall DRD (p = 0.0125), RD (p = 0.005), and ID (p = 0.026). The Hungarian group had a lower overall DRD score (median: 1.29 [1.00; 4.53]) compared to the Romanian group (median: 1.53 [1.00; 5.18]; p <0.05), similarly to the Rroma population (median: 1.44 [1.00; 3.59]); p = 0.018). Similar results were observed for RD across the three ethnicity groups (median: 1.40 [1.00; 5.20] vs 1.80 [1.00; 5.80], p <0.05, and 1.70 [1.00; 4.80]; p = 0.034).

After full adjustment, the GAD-7 score was significantly correlated with the overall DRD (p = 0.0267) and ID (p = 0.0123), while the PHQ-9 score with the overall DRD (p = 0.0013), EB (p <0.0001), and RD (p = 0.0043) (Table 3).

DISCUSSIONS

Being diagnosed with diabetes can be challenging, in part because of the long-term healthcare demands, and because

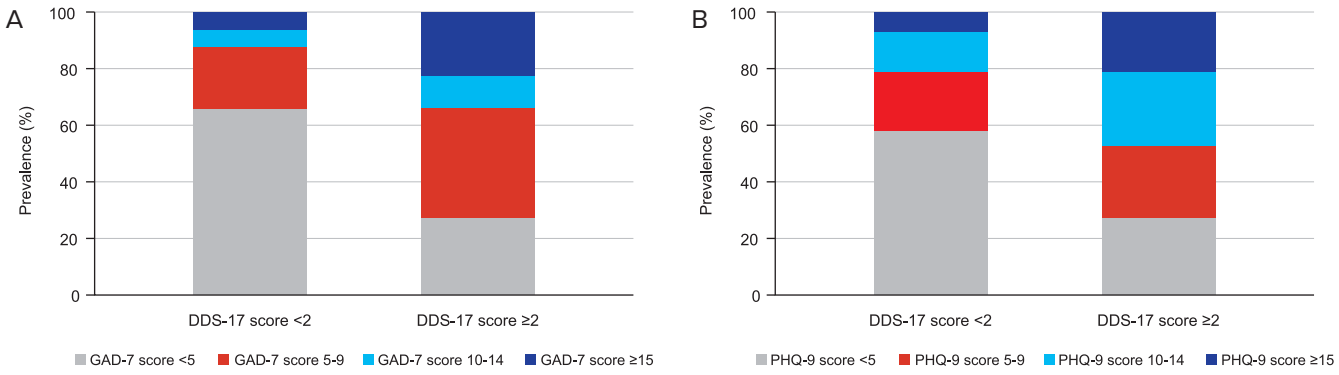

FIGURE 1. Prevalence of generalized anxiety (**A**) and depression (**B**) symptoms (stratified by the degree of severity) in patients with and without DRD

of the progressive nature of the disease, which requires permanent check-ups, adjustments of lifestyle habits, pluri-medication etc. Therefore, it is plausible for someone to develop emotional distress related to the illness, followed by lack of motivation and failure. This study is drawing attention upon the need for psychological evaluation and support for persons with T2DM.

It appears that individuals that present DRD are prone to inadequate glycemic control, and this might be related to reduced interest in a healthy lifestyle, but also poor treatment adherence.[11,24,25] This study results also indicated that patients with DRD had higher HbA1c values. The bivariate analysis showed that both the emotional burden and regimen-related distress positively associated with HbA1c. Additionally, regimen-related distress was positively correlated with fasting blood glucose, although after full adjustment in the multivariate analysis the correlation remained significant for emotional burden. Thus, our study suggests that worse glycemic control is associated rather with emotional distress than poor interpersonal relationships, including with the physician, lack of access to healthcare support, or diabetes regimen. In other words, psychological well-being is an important condition for glycemic control. The question that arises regarding the nature of this interdependence, whether having DRD influences the glycemic outcomes or, on the contrary, higher glycemic values determine certain degrees of emotional distress. The situation is still debatable, and it would need longitudinal evaluation to be clarified. An intervention study in a tertiary-care setting showed a reduction in DRD after a problem-oriented intervention in patients with T2DM, which was also associated with an improvement in metabolic outcomes (HbA1c, blood glucose, insulin units per day, BMI).[26] However, a Cochrane systematic review that included 30 randomized controlled trials (n = 9,177 participants) concluded that psychological intervention did not significantly influence DRD more than usual care. However, the authors suggested a small beneficial effect on self-efficacy and HbA1c (although the quality of evidence was low).[27] A more recent meta-analysis (8 studies, 841 subjects) on the other hand, reported the beneficial effects of mindfulness-based intervention

TABLE 2. The bivariate correlations of the total DDS-17 score and subscales with variables of interest

	Total DDS-17 score	EB score	PD score	RD score	ID score
Age, years	–0.18 [–0.29; –0.06]**	–0.19 [–0.30; –0.07]**	NS	–0.18 [–0.30; –0.06]**	NS
Ethnicity, R vs. H vs. RR	–0.15 [–0.27; –0.03]*	NS	–0.13 [–0.25; –0.005]*	NS	NS
Occupation, A vs. R/UE	–0.15 [–0.26; –0.02]*	–0.15 [0.27; –0.03]*	NS	–0.16 [–0.28; –0.04]**	NS
BMI, kg/m^2	0.12 [–0.0001; 0.24]*	NS	NS	NS	NS
Heart rate, b/min	0.15 [0.03; 0.27]*	NS	0.16 [0.04; 0.27]**	NS	NS
HbA1c, %	0.18 [0.06; 0.30]**	0.19 [0.07; 0.31]**	NS	0.18 [0.06; 0.30]**	NS
Fasting blood glucose, mg/dL	0.15 [0.03; 0.27]*	NS	NS	0.21 [0.09; 0.32]***	NS
GAD-7 score	0.49 [0.39; 0.57]***	0.47 [0.36; 0.56]***	0.20 [0.08; 0.31]***	0.36 [0.25; 0.46]***	0.32 [0.20; 0.43]***
PHQ-9 score	0.49 [0.39; 0.58]***	0.47 [0.37; 0.56]***	0.23 [0.11; 0.34]***	0.37 [0.26; 0.47]***	0.28 [0.16; 0.39]***

Data are presented as r [95% CI]. DDS-17 – Diabetes Distress Scale 17; EB – emotional burden; PD – physician-related distress; RD – regimen-related distress; ID – interpersonal distress; R – Romanian; H – Hungarian; RR – Rroma; A – active; R – retired; UE – unemployed; BMI – body mass index; HbA1c – glycated hemoglobin; GAD-7 – General Anxiety Disorder-7; PHQ-9 – Patient Health Questionnaire-9; NS – not significant statistically; *p <0.05, **p <0.01, ***p <0.001

TABLE 3. The multivariate regression analyses for the total DDS-17 score and each domains score

Variable	Adjusted R2	Regression coefficient [95% CI]	p value
DDS-17 score			
Model 1	7.77%	1.21 [–0.08; 2.50]	0.003
BMI		0.02 [0.001; 0.03]	0.038
Ethnicity		–0.23 [–0.41; –0.05]	0.012
Model 2	26.01%	1.66 [0.49; 2.84]	< 0.0001
Ethnicity		–0.26 [–0.42; –0.10]	0.002
GAD-7 score		0.030 [0.003; 0.06]	0.026
PHQ-9 score		0.041 [0.02; 0.07]	0.001
EB score			
Model 1	10.07%	0.50 [–1.33; 2.34]	0.0002
HbA1c		0.23 [0.10; 0.38]	0.001
BMI		0.03 [0.003; 0.05]	0.028
Model 2	31.73%	1.31 [–0.32; 2.9]	< 0.0001
HbA1c		0.18 [0.05; 0.31]	0.005
PHQ-9 score		0.08 [0.04; 0.11]	< 0.0001
PD score			
Model 1	1.28%	1.38 [0.21; 2.55]	0.754
Model 2	4.25%	1.71 [0.50; 2.93]	0.244
RD score			
Model 1	10.51%	1.32 [–0.38; 3.02]	0.0001
BMI		0.03 [0.01; 0.056]	0.003
Ethnicity		–0.34 [–0.58; –0.10]	0.005
Model 2	22.50%	1.85 [0.24; 3.46]	< 0.0001
Ethnicity		–0.37 [–0.59; –0.14]	0.001
PHQ-9 score		0.05 [0.02; 0.08]	0.004
ID score			
Model 1	2.99%	1.61 [–0.08; 3.30]	0.327
Ethnicity		–0.27 [–0.51; –0.03]	0.026
Model 2	11.16%	1.84 [0.19; 3.49]	0.0003
Ethnicity		–0.30 [–0.53; –0.07]	0.010
GAD-7 score		0.05 [0.01; 0.08]	0.012

The table presents only significant results; for the rest of variables, there were no significant correlations noted. BMI – body mass index; HbA1c – glycated hemoglobin

on HbA1c, depression, stress, and DRD in people with both types of diabetes.[28]

The preliminary analysis in this study indicated a positive correlation between DRD and BMI. Overweight and obesity have been associated with low self-esteem.[29] In fact, weight stigma seems to be associated with several adverse biopsychological outcomes, such as eating disturbances, depression, anxiety, body image dissatisfaction, non-adherence to medication, perceived stress, antisocial behavior, and substance use.[29,30] Therefore, perhaps reducing body weight could be an important factor in overcoming psychological distress, but this needs to be properly evaluated in clinical studies.

In addition, our data suggested an association between DRD and ethnicity. Formal education or economic status did not seem to influence DRD in this study population, and the patients basically had access to the same healthcare facilities/physicians and were from same geographical area. This possibly suggests that cultural differences might impact DRD. These results seem to be in concordance with another study that indicated ethnic disparities related to psychological distress and self-care.[31] Moreover, a culturally tailored diabetes self-management education and support intervention significantly improved psychological distress and self-care.[31]

Among the analyzed variables, the strongest positive correlations with DRD were observed with the PHQ-9 score and the GAD-7 score, respectively ($p < 0.0001$ for both). In fact, patients with clinically meaningful DRD had higher depression and anxiety scores, as well as higher prevalence of moderate/severe symptoms of depression and anxiety. This finding was similar to previous data that found significant correlations with depression (OR: 3; 95% CI 1.8 to 6.4; $r = 0.50$).[32,33]

When analyzing the four DRD domains, it resulted that emotional burden was negatively correlated with age ($p = 0.002$) and professional status ($p = 0.011$) in the bivariate analysis, suggesting that younger, professionally active individuals with T2DM are more prone to develop emotional distress. Our findings are consistent with a study from Vietnam, which revealed that age was negatively associated with the occurrence of overall diabetes-associated distress among DM patients.[10] After full adjustment, the multivariate analysis revealed that HbA1c and depression remained important factors associated with EB. Striving to control blood glucose on the long term (and perhaps, failing sometimes) might indeed bring about feelings of being overwhelmed and fatigued, thus creating an emotional burden.

Physician-related distress was also correlated with the PHQ-9 score ($p = 0.0001$) and the GAD-7 score ($p = 0.001$) in the bivariate analysis, as well as with heart rate and ethnicity. However, in the multivariate analyses, none of the correlations remained significant. It should be noted, however, that the quality of the patient-physician relationship is important for the management of diabetes, as it may influence adherence to treatment.[34] Higher levels of healthcare support were shown to be associated with lower DRD.[11]

The bivariate analysis of our data showed that regimen-associated distress was negatively associated with age and profession, in a similar fashion as DRD, and positively with markers of glycemic control (fasting blood glucose and HbA1c), as well as symptoms of anxiety and depression. Meal planning in relation to antihyperglycemic treatment, clinical and metabolic monitoring, and always follow-

ing recommendations might be overwhelming and tiring sometimes. Previous studies in adults with T2DM pointed out that insulin-treated patients feel more distress than those on oral medication.[10,35] This seems to be related rather to the burden of the insulin regimen and the challenges of reaching glycemic targets.[35] Our data did not indicate an association of RD/DRD with the injectable regimen. We have, however, analyzed oral versus injectable antihyperglycemic agents (insulin and glucagon-like peptide-1 [GLP-1] receptor agonists [RAs]), which might not imply the same level of discomfort and burden, as some of the GLP-1 RAs are administered once a week.

Interpersonal distress was associated with ethnicity and the GAD-7 score in the fully adjusted multivariate analysis ($p < 0.05$ for both), suggesting that generalized anxiety and perhaps sociocultural factors are significant in creating (or easing) the ID. A previous study on 101 patients with T2DM demonstrated that higher perceived support from family members was significantly associated with lower total DRD scores.[36] On the other hand, recent data also showed that not only patients with diabetes are affected by psychological conditions, but also family members (spouses) whom are at higher risk of developing depression/anxiety. The risk is driven by the severity of patient's diabetes.[37]

Our data basically indicated that DRD is prevalent among patients with T2DM and is associated with other neuropsychological disorders such as depression or anxiety. The nature of this interrelation is not clarified yet, therefore further longitudinal studies need to be conducted. This study also emphasizes once more the need to incorporate psychological assessments into clinical practice, and to consider the sociocultural factors when evaluating the DRD. This aspect is of importance as the condition might remain unidentified and therefore untargeted, which may have consequences on healthcare outcomes and quality of life. This also points towards a real need for integrating psychological support for patients (and their families) in the management of T2DM.

CONCLUSIONS

Psychological conditions, such as depression and anxiety, and sociocultural factors like ethnicity significantly contributed to DRD. Worse glycemic control was associated with emotional distress, possibly contributing to it.

CONFLICT OF INTEREST

Nothing to declare.

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REFERENCES

1. Cernea S, Zoltai C, Berbecilă D, Şular FL. Prevalence of Depression, Anxiety and Cognitive Impairment in Patients with Type 2 Diabetes from the Central Part of Romania. *Acta Medica Marisiensis*. 2016;62:209-216.
2. Naicker K, Øverland S, Johnson JA, et al. Symptoms of anxiety and depression in type 2 diabetes: Associations with clinical diabetes measures and self-management outcomes in the Norwegian HUNT study. *Psychoneuroendocrinology*. 2017;84:116-123.
3. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004;27:2154-2160.
4. Zhang Y, Ting RZ, Yang W, et al. Depression in Chinese patients with type 2 diabetes: associations with hyperglycemia, hypoglycemia, and poor treatment adherence. *J Diabetes*. 2015;7:800-808.
5. Carper MM, Traeger L, Gonzalez JS, Wexler DJ, Psaros C, Safren SA. The differential associations of depression and diabetes distress with quality of life domains in type 2 diabetes. *J Behav Med*. 2014;37:501-510.
6. Fisher L, Glasgow RE, Mullan JT, Skaff MM, Polonsky WH. Development of a brief diabetes distress screening instrument. *Ann Fam Med*. 2008;6:246-252.
7. Perrin NE, Davies MJ, Robertson N, Snoek FJ, Khunti K. The prevalence of diabetes-specific emotional distress in people with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2017;34:1508-1520.
8. Chew BH, Mukhtar F, Sherina MS, Paimin F, Hassan NH, Jamaludin NK. The reliability and validity of the Malay version 17-item Diabetes Distress Scale. *Malays Fam Physician*. 2015;10:22-35.
9. Zhang J, Xu C, Wu H, et al. Comparative study of the influence of diabetes distress and depression on treatment adherence in Chinese patients with type 2 diabetes: A cross-sectional survey in the People's Republic of China. *Neuropsychiatr Dis Treat*. 2013;9:1289-1294.
10. Nguyen VB, Tran TT, Dang TL, et al. Diabetes-Related Distress and Its Associated Factors Among Patients with Diabetes in Vietnam. *Psychol Res Behav Manag*. 2020;13:1181-1189.
11. Wardian J, Sun F. Factors associated with diabetes-related distress: implications for diabetes self-management. *Soc Work Health Care*. 2014;53:364-381.
12. Geleta BA, Dingata ST, Emanu MD, Eba LB, Abera KB, Tsegaye D. Prevalence of Diabetes Related Distress and Associated Factors Among Type 2 Diabetes Patients Attending Hospitals, Southwest Ethiopia, 2020: A Cross-Sectional Study. *Patient Relat Outcome Meas*. 2021;12:13-22.
13. Kintzoglanakis K, Vonta P, Copanitsanou P. Diabetes-Related Distress and Associated Characteristics in Patients With Type 2 Diabetes in an Urban Primary Care Setting in Greece. *Chronic Stress (Thousand Oaks)*. 2020;4:2470547020961538.
14. Huynh G, Tran TT, Do THT, et al. Diabetes-Related Distress Among People with Type 2 Diabetes in Ho Chi Minh City, Vietnam: Prevalence and Associated Factors. *Diabetes Metab Syndr Obes*. 2021;14:683-690.
15. Azadbakht M, Taheri Tanjani P, Fadayevatan R, Froughan M, Zanjari N. The prevalence and predictors of diabetes distress in elderly with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2020;163:108133.
16. Kuniss N, Kramer G, Müller UA, et al. Diabetes related distress is high in inpatients with diabetes. *Diabetol Metab Syndr*. 2021;13:40.
17. Asuzu CC, Walker RJ, Williams JS, Egede LE. Pathways for the relationship between diabetes distress, depression, fatalism and glycemic control in adults with type 2 diabetes. *J Diabetes Complications*. 2017;31:169-174.
18. Schmitt A, Bendig E, Baumeister H, Hermanns N, Kulzer B. Associations of depression and diabetes distress with self-management behavior and glycemic control. *Health Psychol*. 2021;40:113-124.
19. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care*. 2015;38(Suppl1):S41-S48.

20. Wong EM, Afshar R, Qian H, Zhang M, Elliott TG, Tang TS. Diabetes Distress, Depression and Glycemic Control in a Canadian-Based Specialty Care Setting. *Can J Diabetes*. 2017;41:362-365.
21. Fisher L, Hessler DM, Polonsky WH, Mullan J. When is diabetes distress clinically meaningful? Establishing cut points for the diabetes distress scale. *Diabetes Care*. 2012;35:259-264.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606-613.
23. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166:1092-1097.
24. Johnson ST, Al Sayah F, Mathe N, Johnson JA. The Relationship of Diabetes-Related Distress and Depressive Symptoms with Physical Activity and Dietary Behaviors in Adults with Type 2 Diabetes: A Cross-Sectional Study. *J Diabetes Complications*. 2016;30:967-970.
25. Kretchy IA, Koduah A, Ohene-Agyei T, Boima V, Appiah B. The Association between Diabetes-Related Distress and Medication Adherence in Adult Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study. *J Diabetes Res*. 2020;1:4760624.
26. Nadine K, Ulrich AM, Christof K, Gunter W, Guido K. Reduction of HbA1c and Diabetes-Related Distress after Intervention in a Diabetes Day Care Clinic in People with Type 2 Diabetes but Not with Type 1 Diabetes. *Exp Clin Endocrinol Diabetes*. 2018;126:242-248.
27. Chew BH, Vos RC, Metzendorf MI, Scholten RJ, Rutten GE. Psychological interventions for diabetes-related distress in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2017;9:CD011469.
28. Ni YX, Ma L, Li JP. Effects of mindfulness-based intervention on glycemic control and psychological outcomes in people with diabetes: A systematic review and meta-analysis. *J Diabetes Investig*. 2021;12:1092-1103.
29. Wu YK, Berry DC. Impact of weight stigma on physiological and psychological health outcomes for overweight and obese adults: A systematic review. *J Adv Nurs*. 2018;74:1030-1042.
30. Papadopoulos S, Brennan L. Correlates of weight stigma in adults with overweight and obesity: A systematic literature review. *Obesity (Silver Spring)*. 2015;23:1743-1760.
31. Pena-Purcell N, Han G, Lee Smith M, Peterson R, Ory MG. Impact of Diabetes Self-Management Education on Psychological Distress and Health Outcomes Among African Americans and Hispanics/Latinos With Diabetes. *Diabetes Spectr*. 2019;32:368-377.
32. Alzughbi T, Badedi M, Darraj H, et al. Diabetes-Related Distress and Depression in Saudis with Type 2 Diabetes. *Psychol Res Behav Manag*. 2020;15:453-458.
33. Chew BH, Vos R, Mohd-Sidik S, Rutten GE. Diabetes-Related Distress, Depression and Distress-Depression among Adults with Type 2 Diabetes Mellitus in Malaysia. *PLoS One*. 2016;11:e0152095.
34. Schoenthaler AM, Schwartz BS, Wood C, Stewart WF. Patient and physician factors associated with adherence to diabetes medications. *Diabetes Educ*. 2012;38:397-408.
35. Tanenbaum ML, Kane NS, Kenowitz J, Gonzalez JS. Diabetes Distress From the Patient's Perspective: Qualitative Themes and Treatment Regimen Differences Among Adults with Type 2 Diabetes. *J Diabetes Complications*. 2016;30:1060-1068.
36. Young CF, Shubrook JH, Valencerina E, et al. Associations Between Social Support and Diabetes-Related Distress in People With Type 2 Diabetes Mellitus. *J Am Osteopath Assoc*. 2020;120:721-731.
37. Nielsen J, Cunningham SA, K Ali M, Patel SA. Spouse's Diabetes Status and Incidence of Depression and Anxiety: An 18-Year Prospective Study. *Diabetes Care*. 2021:dc202652.

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ORIGINAL RESEARCH

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Inflammatory Biomarkers and Endothelial Alteration in Patients with Heart Failure and Acute Coronary Syndromes

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ABSTRACT

Introduction: Systemic inflammation plays a key role in the pathophysiology of acute coronary syndrome (ACS), having a direct effect in promoting the progression and rupture of vulnerable coronary plaques. The aim of this study was to investigate the association between inflammatory biomarkers and the type of ACS (ST-elevation myocardial infarction – STEMI, non-ST-elevation myocardial infarction – NSTEMI, or unstable angina – UA) in patients with confirmed heart failure. **Material and Methods:** This study included a total of 266 patients admitted to the Clinical Department of Cardiology of the County Emergency Clinical Hospital of Târgu Mureș – Cardiac Intensive Care Unit (CICU) for ACS of various types (UA, NSTEMI or STEMI) between January 1, 2017 and December 31, 2020, in whom the diagnosis of heart failure was established based on clinical and paraclinical data. From the total number of patients, 36 were hospitalized for UA and 230 for MI, of which 165 were STEMI and 65 were NSTEMI. **Results:** Only hs-CRP and IL-6 were significantly higher in MI compared to UA. Mean hs-CRP was 4.9 ± 4.5 mg/mL in patients with UA vs. 20.4 ± 42.2 mg/mL in patients with MI ($p = 0.001$), and mean IL-6 was 7.2 ± 13.8 pg/mL in UA vs. 31.6 ± 129.2 pg/mL in MI ($p < 0.0001$). ICAM seems to have had a greater discriminating power between STEMI and other types of ACS in those with heart failure, having a value more than double in those with STEMI (216.1 ± 149.6 ng/mL vs. 448.2 ± 754.4 ng/mL, $p < 0.0001$). **Conclusions:** In patients with heart failure, the increase of inflammatory biomarkers such as hs-CRP is associated with the development of an acute myocardial infarction but not with its type. Adhesion molecules, especially ICAM, are elevated in patients with STEMI compared to other types of ACS, indicating a potential role of endothelial alteration in the development of an ACS when it adds to systemic inflammation linked to heart failure.

Keywords: inflammation, hs-CRP, heart failure, myocardial infarction

INTRODUCTION

Systemic inflammation plays a key role in the pathophysiology of acute coronary syndrome (ACS), having a direct effect in promoting the progression and rupture of vulnerable coronary plaques.[1]

Inflammatory cells and inflammatory mediators produced by these cells are present in the atheromatous plaque before it ruptures, making a major contribution to this cardiovascular event.[2] During the acute event, inflammatory mechanisms contribute to the local tissue repair process at the level of the damaged endothelium, but mediators of inflammation are also present in the coronary or systemic blood flow, probably producing the destabilization of other vulnerable plaques in other coronary territories, a mechanism linked to recurrences of major coronary events. It is well known that about 20% of myocardial infarction (MI) survivors will develop a new ACS in the first year after a heart attack. Systemic inflammatory biomarkers may reflect the severity of inflammation in an ACS. In clinical practice, the most utilized biomarkers of inflammation are C-reactive protein (CRP) and interleukin 6 (IL-6), assays that have been shown to have increased specificity and sensitivity.

Meanwhile, it is known that a myocardial injury of over 15% in the ischemic event leads to altered ventricular function as a consequence of the contractility deficit in the ischemic territory.[3] Recent studies have shown that the most important hemodynamic predictor of long-term mortality after a heart attack is the increase in ventricular volumes following the process of cardiac remodeling, a process directly influenced by inflammatory factors.[4]

Persistence of systemic inflammation after an ACS can cause dilation of the left ventricle, systolic dysfunction, as well as arrhythmic complications.[5] In ACS, myocardial ischemia initially induces a pro-inflammatory response in order to remove necrotic cell debris, and coronary revascularization favors this response. This process is followed by a reparative, anti-inflammatory mechanism (day 4–7), which promotes lesion healing and the formation of scar tissue, preventing myocardial rupture. Disruption of the myocyte balance at this level or alteration of the transition between these two phases can lead to a worsening ventricular remodeling process.[6]

Although the role that inflammation currently plays in the rupture of atheromatous plaques in ACSs and in the unfavorable evolution after MI is well understood, the role of different inflammatory biomarkers in predicting an ACS or its adverse evolution according to the type of ACS (ST-elevation myocardial infarction – STEMI, non-ST-elevation myocardial infarction – NSTEMI, or unstable angina – UA) is less known. Also, the correlation between these inflammatory biomarkers and the type of ACS in the subset of patients who developed heart failure has not yet been investigated.

AIM OF THE STUDY

Assuming that there are pathophysiological differences between the types of ACS, which may shape the impact of systemic inflammation on cardiac function in patients with ACS and ventricular dysfunction, the present study aims to investigate the association between inflammatory biomarkers and the type of ACS (STEMI, NSTEMI, and UA) in patients with confirmed heart failure based on laboratory data (increased values of BNP) or imaging data (reduced ejection fraction).

The first objective was to investigate whether there are differences in inflammatory biomarkers between patients with MI and those with UA, who also suffer from impaired ventricular function concomitantly with ACS.

The second objective was to investigate whether there are differences in inflammatory biomarkers between patients with STEMI and those with other types of ACS (NSTEMI or UA), which also show deterioration of ventricular function concomitantly with ACS.

The third objective was to investigate whether there are differences in inflammatory biomarkers between patients with STEMI and those with NSTEMI, which also show deterioration of ventricular function concomitantly with ACS.

MATERIALS AND METHODS

Study population

This study included a total of 266 patients admitted to the Clinical Department of Cardiology of the County Emergency Clinical Hospital of Târgu Mureș – Cardiac Intensive Care Unit (CICU) for ACSs of various types (STEMI, NSTEMI, and UA) between January 1, 2017 and December 31, 2020, in whom the diagnosis of heart failure was established based on clinical and paraclinical data.

Patients who had any of the following criteria were included in the study:

1. Increased values of BNP, the most accurate biomarker of ventricular dysfunction, the cut-off for this pathology being set at 300 pg/mL for patients in sinus rhythm and at 900 pg/mL for patients with atrial fibrillation.
2. Ejection fraction below 45% determined by echocardiography or MRI.

Of the patients included in the study according to the above criteria, 36 were hospitalized for UA and 230 for MI, of which 165 were STEMI and 65 were NSTEMI.

Blood tests were performed in all patients on day 1 of the onset of ACS, and the following biomarkers were studied: E-selectin, hs-CRP, IL-6, adhesion molecules (VCAM, ICAM), and matrix metalloproteases.

Blood samples were analyzed using the equipment of the Center for Advanced Medical and Pharmaceutical Research of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, as well as those from the Clinical Department of Cardiology of the County Emergency Clinical Hospital of Târgu Mureș. Dry tubes were used for the biochemical tests and EDTA for the blood assay. Biochemical parameters were measured using a Dimension EXL 200 analyzer (Siemens Healthineers, Germany). A Cobas Integra plus analyzer (Roche Diagnostics GmbH, Manheim, Germany) was used to assess the inflammatory profile. A FlexMAP 3D Hardware User system (Luminex Corporation, Neetherlands) was used to quantify the serum level of E-selectin, ICAM, and VCAM. Serum IL-6 and BNP values were quantified using Immulite 2000 XPi equipment (Siemens Healthineers, Erlangen, Germany), as well as the equipment from the Clinical Department of Cardiology.

Statistical analysis

Graph Pad Prism 8.0 software (GraphPad Software Inc., San Diego, USA) was used for statistical analysis. Prior to statistical analysis, all data were checked for normality. The results were expressed as number and percentage, and mean ± standard deviation. Statistical significance, expressed as p, was set at 0.05.

Approval of the ethics committee

The study protocol was approved by the ethics committee of the institution. Prior to any procedure, all participants were informed of the study protocol and gave their informed consent in writing. All study procedures were performed in accordance with the principles set out in the Declaration of Helsinki.

Inflammatory profile assessment

For the analysis of the inflammatory profile that can be correlated with the degree of ventricular dysfunction, 3 types of comparisons were performed:

1. between patients with UA or NSTEMI versus STEMI;
2. between patients with UA versus MI (STEMI and NSTEMI);
3. between patients with NSTEMI versus STEMI.

For administrative reasons, it was not possible to perform the full set of analyses in all patients included in the study, therefore comparisons were performed separately for each analysis.

RESULTS

The comparison of the blood tests of the 238 analyzed patients was made according to the three working hypotheses, on three distinct directions. For administrative reasons it was not possible to perform the complete set of laboratory analysis in all patients included in the study, therefore the total number of determinations was different for each biomarker.

Thus, of the 238 patients with congestive heart failure and ACS included in the study, in 171 patients it was possible to assess hs-CRP and IL-6, in 238 patients it was possible to determine VCAM and ICAM values, in 50 patients it was possible to determine MMP9, and in 159 patients it was possible to determine E-selectin values. The number of measurements for each type of ACS is shown in Table 1.

Inflammatory biomarkers in heart failure and MI (STEMI and NSTEMI) versus UA

Analysis of inflammatory biomarkers in patients with heart failure and MI compared to the group with heart failure and UA shows that among inflammatory biomarkers and adhesion molecules, only hs-CRP and IL-6 are significantly higher in those with MI compared to those with UA. Mean hs-CRP was 4.9 ± 4.5 mg/mL in patients with UA vs. 20.4 ± 42.2 mg/mL in patients with MI ($p = 0.001$), and mean IL-6 was 7.2 ± 13.8 pg/mL in patients with UA vs. 31.6 ± 129.2 pg/mL in patients with MI ($p < 0.0001$).

TABLE 1. Number of measurements of biomarkers for each type of acute coronary syndrome

Biomarkers	Number of measurements			
	UA	NSTEMI	STEMI	Total AMI
hs-CRP (mg/L)	36	46	89	135
IL-6 (pg/mL)	33	41	96	137
VCAM (ng/mL)	8	65	165	230
ICAM (ng/mL)	8	65	235	230
MMP9 (ng/mL)	5	9	36	45
E-selectin (ng/mL)	0	48	108	156

TABLE 2. Comparison of mean values of inflammatory biomarkers in patients with ACS and heart failure, between patients with UA and patients with MI

	UA	AMI	p value
hs-CRP			
n	36	135	0.001
Mean ± SD	4.9 ± 4.5	20.4 ± 42.2	
95% CI	3.3–6.4	13.3–27.6	
IL-6			
n	33	137	<0.0001
Mean ± SD	7.1 ± 13.8	31.6 ± 129.2	
95% CI	2.2–12.0	10.0–53.2	
VCAM			
n	8	230	0.2
Mean ± SD	1176.2 ± 227.0	1122.2 ± 441.4	
95% CI	986.3–1366.0	1065.2–1179.3	
ICAM			
n	8	230	0.2
Mean ± SD	228.4 ± 149.80	382.2 ± 652.0	
95% CI	103.1–353.7	297.9–466.4	
MMP9			
n	5	45	0.5
Mean ± SD	1,832 ± 1082.6	1,579.0 ± 920.7	
95% CI	487.9–3,176.1	1,302.3–1,855.9	

TABLE 3. Comparison of mean values of inflammatory biomarkers in patients with ACS and heart failure, between patients with STEMI and patients with other types of ACS (NSTEMI and UA)

	UA + NSTEMI	STEMI	p value
E-selectin			
n	49	108	0.6
Mean ± SD	73.8 ± 32.7	70.2 ± 29.2	
95% CI	64.4–83.2	64.2–72.7	
hs-CRP			
n	82	89	0.1
Mean ± SD	12.7 ± 32.6	21.2 ± 42.2	
95% CI	5.54–19.9	12.3–30.1	
IL-6			
n	74	96	<0.0001
Mean ± SD	32.2 ± 16.8	23.5 ± 47.3	
95% CI	7.8–70.3	13.9–33.1	
VCAM			
n	73	165	0.09
Mean ± SD	1,185.7 ± 456.7	1,096.7 ± 424.8	
95% CI	1,079.1–1,292.5	1,032.0–1,161.6	
ICAM			
n	73	165	<0.0001
Mean ± SD	216.1 ± 149.6	448.2 ± 754.4	
95% CI	181.1–251.0	333.1–563.3	
MMP9			
n	14	36	0.7
Mean ± SD	1 600.6 ± 796.4	1,605.8 ± 986.0	
95% CI	1,140.9–2,060.4	1,272.0–1,939.7	

In contrast, we found that neither ICAM and VCAM adhesion molecules, known as biomarkers associated with an increased sensibility for vulnerability of atheromatous plaque, nor MMP9 showed significant differences between those with UA and those with MI who also had heart failure.

The mean values of inflammatory biomarkers in patients with heart failure and ACS, analyzed comparatively between the group with UA and the group with MI, are presented in Table 2.

Inflammatory biomarkers in patients with heart failure and STEMI versus other forms of ACS (NSTEMI or UA)

Inflammatory biomarkers in patients with heart failure and STEMI compared with patients with heart failure and other types of ACS (UA and NSTEMI) showed that among inflammatory biomarkers only IL-6 was significantly higher in those with STEMI compared with those with other types of ACS. Thus, the mean value of IL-6 was 32.2 ± 16.8 pg/mL in patients with STEMI, compared with 23.5 ± 47.3 pg/mL in those with other types of ACS. At the same time, ICAM seems to have had a greater discriminating power between STEMI and other types of ACS in those with heart failure, having a value more than double in those with STEMI (216.1 ± 149.6 ng/mL vs. 448.2 ± 754.4 ng/mL, p <0.0001).

The mean values of inflammatory biomarkers in patients with heart failure and ACS, analyzed comparatively between the group with STEMI and the group with NSTEMI or UA, are presented in Table 3 and represented graphically in Figures 1–4.

Inflammatory biomarkers in patients with heart failure and NSTEMI versus STEMI

Inflammatory biomarkers in patients with heart failure and MI (STEMI or NSTEMI) show that only ICAM appeared to have a discriminating power between STEMI and heart failure, having a value more than double in those with STEMI than in those with NSTEMI (214.6 ± 150.6 ng/mL vs. 448.2 ± 754.4 ng/mL, p <0.0001).

The mean values of inflammatory biomarkers in patients with heart failure and ACS, analyzed comparatively between the group with STEMI and the group with NSTEMI, are presented in Table 4.

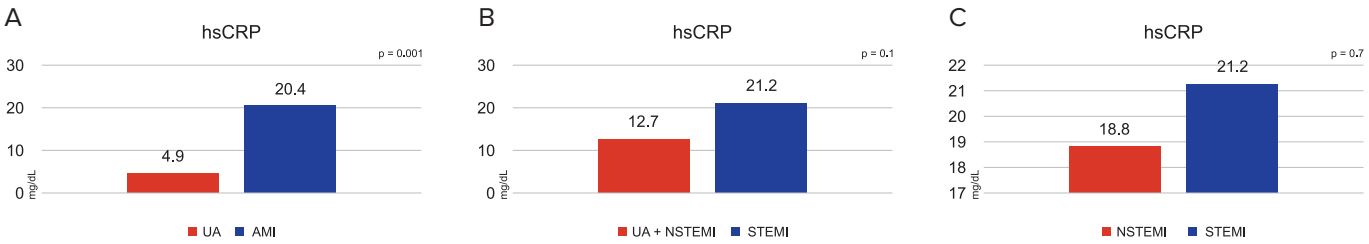

FIGURE 1. Mean values of hs-CRP in patients with heart failure and **A** – UA vs. AMI; **B** – STEMI vs. other forms of ACS; **C** – STEMI vs. NSTEMI

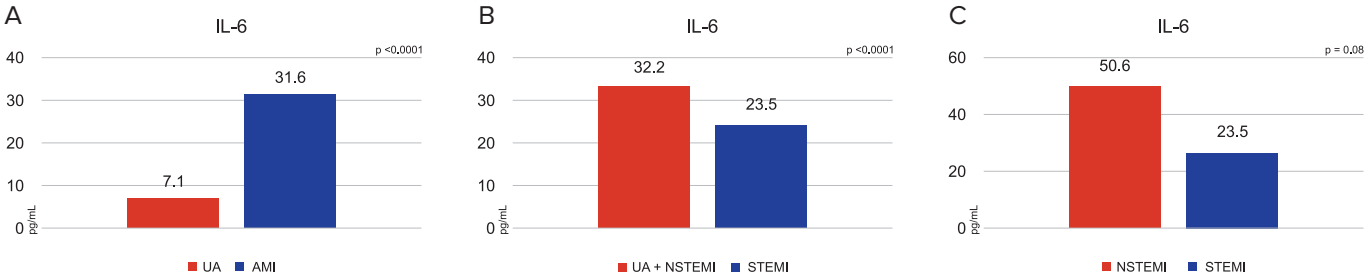

FIGURE 2. Mean values of IL-6 in patients with heart failure and **A** – UA vs. AMI; **B** – STEMI vs. other forms of ACS; **C** – STEMI vs. NSTEMI

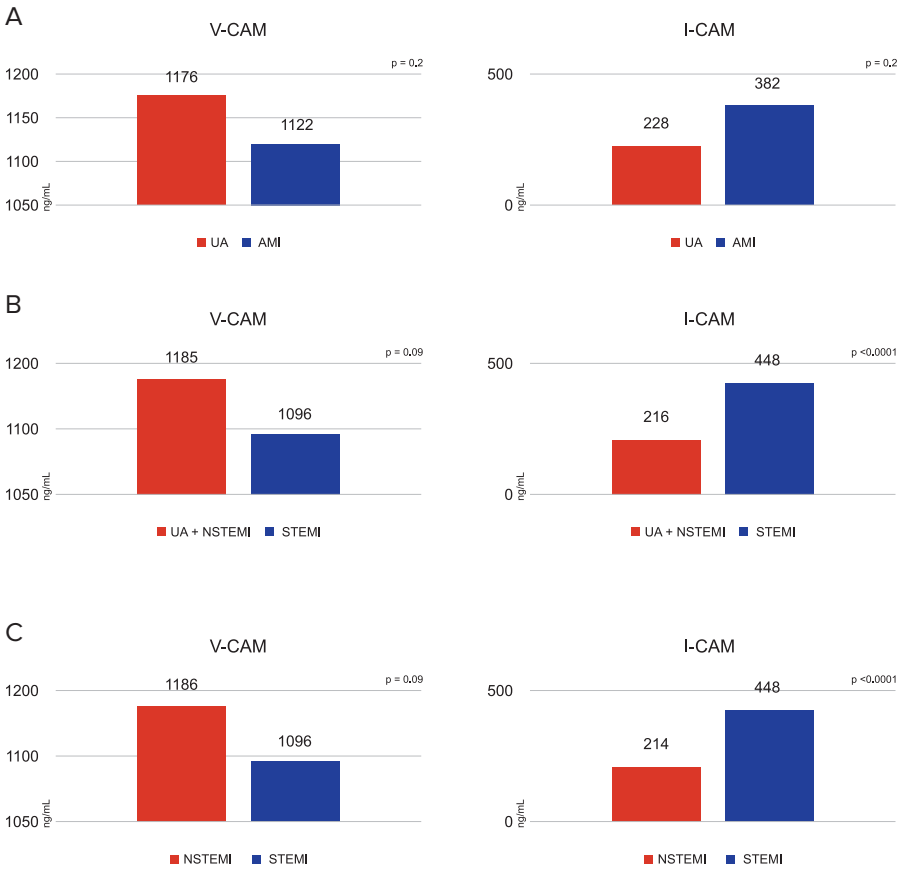

FIGURE 3. Mean values of adhesion molecules (VCAM and ICAM) in patients with heart failure and **A** – UA vs. AMI; **B** – STEMI vs. other forms of ACS; **C** – STEMI vs. NSTEMI

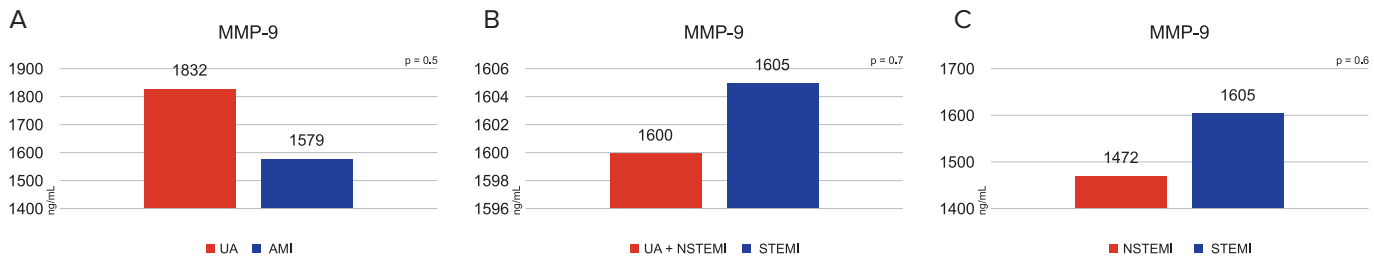

FIGURE 4. Mean values of MMP9 in patients with heart failure and **A** – UA vs. AMI; **B** – STEMI vs. other forms of ACS; **C** – STEMI vs. NSTEMI

DISCUSSION

The vulnerable plaque is an atherosclerotic lesion very prone to rupture. This rupture increases the risk of atherothrombosis and also the development of an ACS.[7,8] The concept of vulnerable plaque was introduced as an explanation for the sudden change of the clinical course of atherosclerosis, as a result of structural modifications that may occur in the atheromatous plaques. The vulnerable plaque hypothesis was developed in an effort to better describe the unpredictability of the clinical course of atherosclerosis. Vulnerable plaques have been defined as "culprit" lesion (the plaque that causes occlusion), causing acute vascular events or death, regardless of shape, stenosis, or stage of destabilization.[9–12]

TABLE 4. Comparison of mean values of inflammatory biomarkers in patients with ACS and heart failure, between patients with STEMI and patients with NSTEMI

	NSTEMI	STEMI	p value
E-selectin			
n	48	108	0.8
Mean ± SD	73.0 ± 32.5	70.2 ± 29.2	
95% CI	63.5–82.4	64.2–72.7	
hs-CRP			
n	46	89	0.7
Mean ± SD	18.8 ± 42.5	21.2 ± 42.2	
95% CI	6.1–31.5	12.3–30.1	
IL-6			
n	41	96	0.08
Mean ± SD	50.6 ± 225.6	23.5 ± 47.3	
95% CI	20.5–121.8	13.9–33.1	
VCAM			
n	65	165	0.9
Mean ± SD	1,186.9 ± 478.6	1,096.7 ± 424.8	
95% CI	1,068.3–1,305.6	1,032.0–1,161.6	
ICAM			
n	65	165	<0.0001
Mean ± SD	214.6 ± 150.6	448.2 ± 754.4	
95% CI	177.2–251.9	333.1–563.3	
MMP9			
n	9	36	0.6
Mean ± SD	1,472.1 ± 626.5	1,605.8 ± 986.0	
95% CI	990.5–1,953.7	1,272.0–1,939.7	

Early detection of plaque stage before it becomes unstable is still a challenge. In recent years, invasive and non-invasive techniques have been developed to determine the evolution of a plaque and also to develop new therapies in order to reduce the risk of rupture and its consequences. In addition to imaging investigations, research into biomarkers for staging and prevention of ACS and stroke has become a subject in vulnerable plaque theory. Various markers that reflect inflammatory activity, matrix degradation, lipid metabolism, and platelet activity are investigated.[8,13–15]

Atherogenesis may be triggered by the alteration of endothelial structures, leading to an increased expression of adhesion molecules, an important role being played by systemic inflammation. Endothelial lesions may lead to expression of VCAM and ICAM molecules, allowing leukocytes to adhere to the endothelial lesion, favoring chemokine accumulation, metalloproteinase secretion, and plaque rupture.[16]

In this study, particularly in patients with heart failure, the influence of systemic inflammation was related especially to differentiation between patients with MI and those with UA. Serum levels of both inflammatory biomarkers (hs-CRP and IL-6) were significantly higher levels in patients with myocardial infarction (20.4 ± 42.2 mg/mL vs. 4.9 ± 4.5 mg/mL, p = 0.001 for hs-CRP, and 31.6 ± 129.2 pg/mL vs. 7.1 ± 13.8 pg/mL, p <0.0001 for IL-6). At the same time, molecular adhesion biomarkers showed no significant difference between patients with MI and those with UA.

Interestingly, biomarkers expressing endothelial alterations, and especially ICAM, seem to be significantly higher in patients with STEMI compared to other types of ACS. In our study, ICAM values were significantly higher in the

STEMI group compared with NSTEMI patients (448.2 ± 754.4 ng/mL vs. 214.6 ± 150.6 ng/mL, p <0.0001). This association has not been described so far in the general group of patients with ACS, being particularly relevant in this study which included only patients with heart failure.

On the other hand, serum values of inflammation biomarkers in the clinical context of the patient with heart failure and ACS may be influenced by a large number of factors, since heart failure itself may increase systemic inflammation and thus the serum levels of inflammatory biomarkers.[17] Since there were no significant differences in inflammatory biomarkers between the STEMI and NSTEMI groups, it may be concluded that the increase of inflammatory status and biomarkers caused by heart failure may preclude a clear and unbiased correlation between inflammatory biomarkers and the type of infarction. Endothelial alterations expressed by ICAM-type biomarkers seem to play a more significant role on the complex mechanism of coronary plaque vulnerabilization in patients with heart failure.

CONCLUSIONS

In patients with heart failure, the increase of inflammatory biomarkers such as hs-CRP is associated with the development of an acute myocardial infarction but not with its type. Adhesion molecules, especially ICAM, are elevated in patients with STEMI compared to other types of acute coronary syndromes, indicating a potential role of endothelial alteration in the development of an acute coronary syndrome when it adds to systemic inflammation linked to heart failure.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Ramakrishnan AV, Varghese TP, Vanapalli S, Nair NK, Mingate MD. Platelet activating factor: A potential biomarker in acute coronary syndrome? *Cardiovascular Therapeutics*. 2017;35:64-70.
2. Ma CY, Xu ZY, Wang SP, Peng HY, Liu F, Liu JH, Ren FX. Change of Inflammatory Factors in Patients with Acute Coronary Syndrome. *Chin Med J (Engl)*. 2018;131:1444-1449.
3. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, et al. Inflammation Following Acute Myocardial Infarction: Multiple Players, Dynamic Roles, and Novel Therapeutic Opportunities. *Pharmacology & Therapeutics*. 2018;186:73-87.
4. Fang L, Moore XL, Dart AM, Wang LM. Systemic inflammatory response following acute myocardial infarction. *Journal of Geriatric Cardiology*. 2015;12:305-312.
5. Nian M, Lee P, Khaper N, Liu P. Inflammatory Cytokines and Postmyocardial Infarction Remodeling. *Circulation Research*. 2004;94:1543-1553.
6. Milano SS, Victorino de Mourna O, Bordin AAS, Marques GL. C-Reactive Protein Is a Predictor of Mortality in ST-Segment Elevation Acute Myocardial Infarction. *International Journal of Cardiovascular Sciences*. 2019;32:118-124.
7. Benedek T. Imaging Vulnerable Plaque in a Modern School of Cardiology – the PlaqueImage Project. *Journal of Interdisciplinary Medicine*. 2021;6:1-2.
8. Stefanadis C, Antoniou CK, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. *J Am Heart Assoc*. 2017;17:e005543.
9. Li JJ, Fang CH. Atherosclerotis is a more rational term for the pathological entity currently known as atherosclerosis. *Med Hypotheses*. 2004;63:100-102.
10. Seidman M, Mitchell R, Stone J. Cellular and Molecular Pathobiology of Cardiovascular Disease. Cambridge, MA: Academic Press, 2014; p. 221-237.
11. Kumar V, Abbas KA, Aster J. Robbins Basic Pathology. 10th ed. Philadelphia, PA: Elsevier - Health Sciences Division, 2017; p. 335-343.
12. Groh L, Keating ST, Joosten LAB, et al. Monocyte and macrophage immunometabolism in atherosclerosis. *Semin Immunopathol*. 2018;40:203-214.
13. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664-1672.
14. Hafiane A. Vulnerable Plaque, Characteristics, Detection, and Potential Therapies. *J Cardiovasc Dev Dis*. 2019,6(3):26.
15. Gerculy R, Mitra N, Szabó E, Opincariu D, Chițu M, Benedek I. Management of Culprit and Non-Culprit Lesions in Acute Coronary Syndrome. *Journal of Interdisciplinary Medicine*. 2021;6:32-36.
16. Gonçalves I, Ruijter H den, Nahrendorf M, Pasterkamp G. Detecting the vulnerable plaque in patients. *Journal of Internal Medicine*. 2015;278:520-530.
17. Benedek T. The Link between Periodontal Disease, Inflammation and Atherosclerosis — an Interdisciplinary Approach. *Journal of Interdisciplinary Medicine*. 2017;2(S1):11-16.

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ORIGINAL RESEARCH

ORTHOPEDICS // RADIOLOGY

Correlation between Magnetic Resonance Imaging and Arthroscopic Findings in Knee Lesions

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ABSTRACT

Background: Magnetic resonance imaging (MRI) is a noninvasive diagnostic method with no known side effects and a high sensitivity for detecting meniscal lesions as well as lesions of the anterior and posterior cruciate ligaments. For a correct and complete diagnosis, MRI results must be interpreted in the context of clinical examination and anamnesis. MRI results can support the surgical indication for arthroscopy, which is a minimally invasive intervention that facilitates the visualization, investigation, diagnosis, and treatment of intra-articular lesions of the knee. The purpose of this study was to assess the correlation between MRI results and the intra-articular lesions detected arthroscopically. **Material and methods:** This retrospective study evaluated a total of 60 patients admitted and treated between January 1, 2013 and January 1, 2014 in the Clinic of Orthopedics and Traumatology of Mureș County Hospital, Târgu Mureș, Romania. **Results:** In the 43 patients with lesion of the anterior cruciate ligament, the lesions were seen on MRI in 40 patients (93%) and confirmed arthroscopically in 37 patients (86%). In 34 cases (79.1% of the total of 43), the MRI and arthroscopic results were similar, the Kappa coefficient showing a high degree of correlation (0.90). **Conclusion:** By assessing the Kappa coefficient to highlight the correlation between MRI results and arthroscopic diagnosis for knee injuries, a statistically relevant correlation between the two methods was found. This suggests that a correct diagnosis can be achieved by both methods.

Keywords: knee, intra-articular lesions, magnetic resonance imaging, arthroscopy

INTRODUCTION

Knee injuries are most commonly encountered as a result of traumas suffered at this level and are frequent because of the increasing popularity of sports such as football, basketball, and skiing in our country. The severity of these lesions depends equally on localization, stretching, physical condition, and muscle strength. Multiple efforts have been made to evaluate the amount of disability

caused by injuries to knee structures and the success of their treatment by conservative or surgical methods.

Magnetic resonance imaging (MRI) has been successfully used to diagnose knee lesions for more than 20 years and has often been regarded as the noninvasive alternative of diagnostic arthroscopy. Numerous large studies have evaluated the diagnostic capabilities of MRI, with varied outcomes. In day-to-day clinical practice, MRI is routinely used to support the diagnosis of meniscal or ACL injuries prior to recommending arthroscopic examination and surgery. The identification of meniscal tears can be difficult to interpret and depends on both the observer and the sensitivity of the scanner. Similar difficulties may exist in clinical examination as well. The arthroscope provides an easy method to examine the interior of the knee; it provides a good view of the patello-femural joint and is associated with a very low morbidity. The role of arthroscopic examination in the diagnosis of knee problems has been reported many times. Since Burman's description of the use of an arthroscope to visualize joints in a cadaveric model, arthroscopy has risen in popularity to become the most commonly performed orthopedic procedure today. Despite the diverse applications of arthroscopy to examine the shoulder, ankle, wrist, and hip, arthroscopy of the knee has remained the most frequently performed procedure.

Considering that arthroscopy is one of the two major interventions of the last century in orthopedic surgery and MRI is the gold standard paraclinical investigation in knee injuries, the aim of this work was to highlight the correlation between the two methods. For each type of lesion, we aimed to investigate whether they are described both in the operative protocol and the radiological results.

MATERIAL AND METHODS

A retrospective observational study was conducted during a 12-month period in the Clinic of Orthopedics and Traumatology of Mureș County Hospital, Târgu Mureș, Romania. A total of 60 patients were evaluated. In order to make an objective comparison between the two methods and to reach a conclusion that could be of practical significance, these study assessed lesions of several anatomical structures such as the posterior cruciate ligament (PCL), anterior cruciate ligament (ACL), medial collateral ligament (MCL), medial meniscus, lateral meniscus, persistent vertical septum, reactive synovitis, Baker's cyst, and cartilage lesions.

Patients with the above mentioned knee injuries, aged between 15 and 60 years, who underwent an MRI scan and arthroscopic surgery were included in the study.

TABLE 1. K value

K value	Degree of agreement
<0.20	Slight
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Substantial
0.81–1.00	Almost perfect

Patients with contraindications for MRI (intracerebral aneurysmal clips, cardiac pacemakers, metallic foreign body in the eyes, or middle ear implants), patients with recent knee injury but with no instability in any plane on the clinical examination and negative McMurray test, as well as patients who were unfit for anesthesia were excluded from the study.

A blinded radiologist reported the MRI findings. All arthroscopic procedures were performed in a standard manner by an experienced arthroscopic surgeon, under spinal anesthesia. The diagnostic findings were compared at one level: MRI versus arthroscopic findings.

Statistical analysis

As a statistical method, we used the Kappa coefficient, which indicates the power of agreement between the two diagnostic methods. Kappa scores take into account the ordering of categorical variables (Table 1). A weighted Kappa score that evaluates agreement between MRI and arthroscopy findings was calculated through a matrix in which MRI ratings were arrayed in the rows and arthroscopy ratings in the columns. The calculation was based on the difference between how much agreement was actually present compared to how much agreement would be expected by chance alone. In our study, the coefficient was calculated using the Statistical Package for Social Sciences (SPSS) for Windows (Armonk, NY: IBM Corp, USA). The Mann-Whitney test was used to analyze demographic data.

The study was conducted in accordance with the principles stipulated in the Declaration of Helsinki. Informed consent was waived by the ethics committee of the Mureș County Hospital.

RESULTS

Baseline demographics and patient characteristics show an average age of 32.8 ± 11.41 years (range 15–59 years). Patient gender had an almost equal distribution: 48.3% (n = 29) were women and 51.7% (n = 31) men. The demo-

graphic data showed no significant differences between the two groups.

Patients included in the study were suffering from knee trauma due to injuries from skiing, football, or falling from the same level, most of them being young patients. Most of the patients (43 out of 60) presented with ACL injuries. Only two patients presented with PCL injuries, diagnosed by both MRI and arthroscopy. As far as meniscus lesions are concerned, most of the subjects (44 out of 60) presented with medial meniscus injuries, and 28 presented with lateral meniscus trauma.

Persistent vertical septum and Baker's cyst were predominantly highlighted by MRI descriptions. Also, it is noteworthy that reactive synovitis was only described in the arthroscopy protocol.

ACL lesions were described on the MRI examination in 40 patients (93%) and were confirmed arthroscopically in 37 patients (86%). In 34 cases (79.1%), the MRI and arthroscopic results were similar, the Kappa coefficient showing a high degree of correlation (0.90). Only two patients were identified with a PCL lesion by MRI and arthroscopy. Medial meniscus lesions (anterior and posterior horns) were seen on MRI in 43 patients (97.7%) and arthroscopically in 41 patients (93.2%). In 40 cases (90.9% from the total of 44) there was an agreement between the two methods regarding the diagnosis, the Kappa coefficient showing a degree of correlation of 0.96.

Regarding the body of the medial meniscus, the lesion was detected by MRI in nine patients (81.8%) and arthroscopically in nine patients (81.8%). In seven cases (77.8% from the total of 11), there was an agreement between the two methods, the Kappa coefficient showing a correlation of 0.78, which is considered good.

For the whole medial meniscus (body, anterior and posterior horn), the lesion was detected by MRI in 43 patients (97.7%) and by arthroscopy in 42 patients (95.5%). In 41 cases (93.2% from the total of 44) there was an agreement between the two methods, the Kappa coefficient showing a degree of correlation of 0.96.

Lateral meniscus injuries (body, anterior and posterior horns) were found by MRI in 23 patients (82.1%) and by arthroscopy in 21 patients (75%). In 16 cases (57.1% from the total of 28) the diagnosis was concordant between the two methods, the Kappa coefficient of 0.74 indicating a good level of agreement.

In the case of persistent vertical septum, the lesion was detected by MRI in nine patients (69.2%) and by arthroscopy in 13 patients (100%). In nine cases (69.2% from the total of 13) the diagnosis was the same for both methods. The Kappa coefficient could not be calculated.

Baker's cyst was highlighted via MRI in six patients (85.7%) and via arthroscopy in only one patient (14.3%). This case was also confirmed by MRI. However, the Kappa coefficient of 0.54 indicated a moderate level of agreement.

For cartilage lesions, the injury was found by MRI in 11 patients (29.7%), and by arthroscopy in 37 patients. All cases diagnosed by MRI were confirmed by arthroscopy. The Kappa coefficient could not be calculated either for cartilage lesions or for reactive synovitis and lesions of the MCL.

DISCUSSIONS

Most MRIs were performed in clinics from Târgu Mureș. In order to have more precise data on the sensitivity and specificity of the MRI procedure, a protocol should be established that includes the following information: a detailed patient history, a complete clinical examination, MRI and, if appropriate, an arthroscopic report.

In some situations, the Kappa coefficient of agreement could not be calculated because the number of patients presenting these conditions was insufficient, and the images were depicted on MRI and also arthroscopy. There are numerous studies in recent years addressing this issue, trying to determine which diagnostic method is more accurate.[1–23] A study on 36 patients evaluated the accuracy of MRI in the diagnosis of cartilage lesions in comparison with arthroscopy.[15] The results suggested that MRI descriptions can show cartilage damage, but cannot assess the severity of the cartilage injury, the study concluding that arthroscopy remains the most accurate diagnostic method.

Another study, conducted on 185 subjects, compared the diagnostic accuracy of MRI and arthroscopy in ACL and meniscus ruptures.[10] This study also concluded that arthroscopy was the most accurate diagnostic method, and even a rigorous clinical examination was more reliable than the MRI examination.[10]

Comparing the accuracy of the two methods in diagnosing meniscal lesions, a study conducted on 70 patients found that a clinical examination was at least as suggestive (or even more suggestive in some situations) as MRI images.[11] The study stressed the importance of clinical examination, which depends on the experience of the surgeon, who in turn relies heavily on the images acquired by arthroscopy. MRI is considered useful when there is a clinical suspicion for a type of lesion but the question arises whether or not to intervene arthroscopically.[11–15]

In another study, the authors aimed to quantify the ability of 3.0 Tesla MRI to detect articular cartilage lesions at the level of the knee.[9] Joint lesions observed on MRI were grad-

ed from 1 to 4 and compared with the grades of the Outerbridge classification and those of the International Cartilage Repair Society (ICRS), used in arthroscopic imaging. The articular surface was divided into six regions. However, one limitation consisted in the fact that the MRI assessments were performed by more than one operator, without establishing a coefficient of variance for each lesion.[9] Based on the MRI images, from a total of 288 joints, 113 (39%) had a positive diagnosis (from grade 2 to 4). The Kappa coefficient applied to the MRI examination, the Outerbridge, and the ICRS classification was 0.13, 0.54, and 0.63, respectively. When using the ICRS and the Outerbridge classification on MRI, the sensitivity, specificity, and accuracy were 54%, 92%, and 75%, respectively. Based on these results, the authors concluded that 3.0 Tesla MRI did not show a significant power in diagnosing cartilage lesions.[9]

CONCLUSIONS

Out study found a good correlation between MRI and arthroscopy in assessing lesions of the anterior cruciate ligament, medial meniscus, and lateral meniscus. In case of Baker's cyst, there was a moderate diagnostic agreement between the two methods. In the rest of the cases, namely lesions of the posterior cruciate ligament and medial collateral ligament, the existence of reactive synovitis, the persistence of the vertical septum, and cartilage lesions, the Kappa coefficient could not be calculated due to the reduced number of subjects. However, the lesions were mainly diagnosed on MRI, except for reactive synovitis, which was diagnosed only by arthroscopic imaging. In order to assert a correct and complete diagnosis, MRI should be interpreted in the context of a thorough anamnesis and clinical examination. As a final conclusion, there is a strong correlation between the diagnostic power of the compared methods, thus both can be used for a correct diagnosis.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Bruyère O, Burlet N, Delmas PD, Rizzoli R, Cooper C, Reginster JY. Evaluation of symptomatic slow-acting drugs in osteoarthritis using the GRADE system. *BMC Musculoskeletal Disorders*. 2008;11:165.
2. Gidwani S, Fairbank A. The orthopaedic approach to managing osteoarthritis of the knee. *BMJ*. 2004;11:1220-1224.
3. Gross AE. Cartilage resurfacing: filling defects. *J Arthroplasty*. 2003;11:14-17.
4. Hunziker EB. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. *Osteoarthritis Cartilage*. 2002;11:432-463.
5. Disler DG, McCauley TR, Kelman CG, et al. Fat-suppressed three-dimensional spoiled gradient-echo MR imaging of hyaline cartilage defects in the knee: comparison with standard MR imaging and arthroscopy. *Am J Roentgenol*. 1996;11:127-132.
6. Halbrecht JL, Jackson DW. Office arthroscopy: a diagnostic alternative. *Arthroscopy*. 1992;11:320-326.
7. Mathieu L, Bouchard A, Marchaland JP, et al. Knee MR-arthrography in assessment of meniscal and chondral lesions. *Orthop Traumatol Surg Res*. 2009;11:40-47.
8. Dzoleva-Tolevska R, Poposka A, Samardziski M, Georgieva D. Comparative analysis of diagnostic methods in meniscal lesions. *US National Library of Medicine, Prilozi*. 2013;34:79-84;
9. Reed ME, Villacis DC, Hatch GH, Burke WS. 3.0-Tesla MRI and arthroscopy for assessment of knee articular cartilage lesions. *Orthopedics*. 2013;36:e1060-4.
10. Bisson LJ, Kluczynski MA, Hagstrom LS, Marzo JM. A prospective study of the association between bone contusion and intra-articular injuries associated with acute anterior cruciate ligament tear. *Am J Sports Med*. 2013;41:1801-1807.
11. Siddiqui MA, Ahmad I, Sabir AB. Clinical examination vs. MRI: evaluation of diagnostic accuracy in detecting ACL and meniscal injuries in comparison to arthroscopy. *Pol Orthop Traumatol*. 2013;78:59-63.
12. Notohamiprodjo M, Horng A, Kuschel B, Paul D. 3D-imaging of the knee with an optimized 3D-FSE-sequence and a 15-channel knee-coil. *Eur J Radiol*. 2012;81:3441-3449.
13. Ercin E, Kaya I, Sungur I, Demirbas E. History, clinical findings, magnetic resonance imaging and arthroscopic correlation in meniscal lesions. *Knee Surg Sports Traumatol Arthrosc*. 2012;20:851-856.
14. Magarelli N, Carducci C, Cannataro G. MR in the evaluation of new anterior cruciate ligament and tibial tunnel position: correlation with clinical and functional features. *Radiol Med*. 2011;116:1124-1133.
15. von Engelhardt LV, Lahner M, Klussmann A. Arthroscopy vs. MRI for a detailed assessment of cartilage disease in osteoarthritis: diagnostic value of MRI in clinical practice. *BMC Musculoskelet Disord*. 2010;11:75.
16. Böttcher P, Brühschwein A, Winkels P. Value of low-field magnetic resonance imaging in diagnosing meniscal tears in the canine stifle: a prospective study evaluating sensitivity and specificity in naturally occurring cranial cruciate ligament deficiency with arthroscopy as the gold standard. *Vet Surg*. 2010;39:296-305.
17. Notohamiprodjo M, Horng A, Pietschmann MF, Müller PE. MRI of the knee at 3T: first clinical results with an isotropic PDfs-weighted 3D-TSE-sequence. *Invest Radiol*. 2009;44:585-597.
18. Esparragoza-Montero R, Rodriguez-Diaz J, Lanier-Dominguez J. Evaluation of meniscal morphology and relation between the diagnostic findings of magnetic resonance imaging and arthroscopy in lesions of the knee. *Invest Clin*. 2009;50:35-44;
19. Rayan F, Bhonsle S, Shukla DD, Clinical. MRI, and arthroscopic correlation in meniscal and anterior cruciate ligament injuries. *Int Orthop*. 2009;33:129-132.
20. Mughetti M, De Masi M, Teodorani A. Computerized tomography false positives in knee medial meniscus injuries. Retrospective study of 400 cases. *Radiol Med*. 1998;96:310-312.
21. Brossmann J, Muhle C, Büll CC, Schröder C. Evaluation of patellar tracking in patients with suspected patellar malalignment: cine MR imaging vs arthroscopy. *AJR – Am J Roentgenol*. 1994;162:361-367;
22. Broderick LS, Turner DA, Renfrew DL. Severity of articular cartilage abnormality in patients with osteoarthritis: evaluation with fast spin-echo MR vs arthroscopy. *AJR – Am J Roentgenol*. 1994;162:99-103;
23. Tung GA, Davis LM, Wiggins ME. Tears of the anterior cruciate ligament: primary and secondary signs at MR imaging. *Radiology*. 1993;188:661-617.

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CASE SERIES

PNEUMOLOGY // ALLERGOLOGY

The Benefit of Benralizumab Monoclonal Antibody Treatment for Severe Eosinophilic Asthma in a Case Series (Pulmonology Clinic Târgu Mureș, Romania)

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ABSTRACT

Background: Monoclonal antibody therapy is currently an additional treatment option to reduce exacerbations and improve symptom control in patients with severe eosinophilic asthma (SEA) that is uncontrolled despite treatment with high-dose inhaled corticosteroids and long-acting beta-2 agonists. Benralizumab, a monoclonal antibody that binds to the interleukin-5 receptor (IL-5), significantly reduces symptoms and annual exacerbations, as well as the use of systemic corticosteroids in patients with SEA. However, few studies are available on the effectiveness of this biological treatment in real life. The aim of this case series was to evaluate the efficacy of benralizumab by analyzing changes in clinical parameters and blood eosinophils in patients with SEA. **Methods:** We analyzed four patients with SEA who started treatment with benralizumab. The history of symptoms and exacerbations, eosinophil counts, data regarding the oral corticosteroid dose, need for rescue treatment, spirometry measurements and asthma control questionnaires (ACT) regarding the level of asthma control were recorded. A positive response to treatment was defined by a significant reduction in eosinophil counts, increased ACT scores, and lower rates of exacerbations. **Results and conclusions:** Benralizumab monoclonal antibody was effective in all four patients. This was shown by a reduction in exacerbation rates, symptom severity, and lower dose of oral corticosteroids and rescue medication. This novel treatment was well tolerated by the analyzed patients, thus indicating that benralizumab is an attractive choice for patients due to eosinophilic count reduction as well as the less frequent dosing schedule. However, further studies are required, on larger populations.

Keywords: monoclonal antibody therapy, severe eosinophilic asthma, clinical parameters, eosinophils

INTRODUCTION

Severe eosinophilic asthma (SEA) is defined by remaining uncontrolled despite maximum optimal treatment (with good adherence and inhalation technique but also with the control of contributing factors) in advanced stages, or worsening symptoms despite treatment with inhaled corticosteroids.[1] About 3–10% of people with asthma have SEA.[2]

SEA carries a great burden on affected patients, with a significant decrease in the quality of life due to frequent exacerbations, disability, and increased mortality rates. In addition, SEA is also a social and economic problem for patients and their families due to increased healthcare costs related to treatment, frequent emergency presentations, imaging and laboratory testing, but also indirectly due to temporary or permanent loss of working ability.[3]

Monoclonal antibodies, such as benralizumab, are among the newest therapeutic options for severe asthma. This medication is added to general measures (education, preventive measures for exacerbations) and to the daily maintenance therapy. Monoclonal antibodies have long-term beneficial effects including increased symptoms control, reduced use of systemic corticosteroids and rescue medication, and decreased number and severity of exacerbations. Benralizumab has shown therapeutic benefits in patients over 12 years of age and in adults with SEA that is not adequately controlled by inhaled high-dose corticosteroids in combination with long-acting beta-agonists.[4]

Benralizumab binds to the alpha subunit of the IL-5 receptor (from eosinophils or basophils involved in asthmatic inflammatory response), thus leading to cell apoptosis and cell death by attracting natural killer T cells. This action significantly reduces the asthma inflammatory response mediated by eosinophils. Benralizumab has effects on symptom control, reduced exacerbations, improved lung function and quality of life in patients with SEA.[5,6]

Benralizumab is administered by subcutaneous injection (30 mg) every 4 weeks (first 3 doses) and then 1 dose every 8 weeks. Studies have shown that one intravenous dose and several subcutaneous ones reduce the number of eosinophils in the bronchial mucosa/submucosa, but also in the bone marrow and peripheral blood.[6]

The depletive effect of blood eosinophils is established within the first 24 hours after the first dose, and the effect is maintained throughout the treatment period. The depletion of blood eosinophils is accompanied by a reduction in eosinophilic granular proteins – eosinophil-derived neurotoxin (EDN) and eosinophilic cationic protein (ECP) – but also by a reduction in the number of blood basophils.[7]

Eligibility criteria for benralizumab include patients with SEA (correctly treated in steps 4–5 of the GINA classification), with multiple exacerbations in the last year and elevated peripheral blood eosinophil count ≥300 elements/μL). Patients taking oral corticosteroids (OCS) with corticoid-dependent asthma are a well-indicated group given the known risk of long-term side effects of systemic corticosteroids.[8]

The aim of the manuscript was to conduct a case series study to evaluate the effect of benralizumab on patients with SEA, despite optimal medical treatment, by analyzing eosinophil blood count and the patients' quality of life.

MATERIALS AND METHODS

We prospectively analyzed four SEA patients who were under observation and treatment in the Pulmonology Clinic of Târgu Mureș, Romania, in 2019. The results of the present manuscript illustrate the preliminary results of a larger study conducted in 2019. Inclusion criteria were the following: age over 18 years and severe asthma which remains uncontrolled despite maximum optimal treatment, with elevated blood eosinophil count ≥300 elements/μL and multiple exacerbations in the last year. Exclusion criteria consisted of patients under 18 years, blood eosinophils <300 elements/μL, Asthma Control Questionnaire (ACT) score over 21. The study was conducted in accordance with the principles stipulated in the Declaration of Helsinki. All subjects agreed with processing of their data, and the study procedures were carried out following approval of the institution where the patients were treated.

CASE SERIES

Case no. 1

We present the case of a 68-year-old patient, former smoker (34 packs/year), with a body mass index (BMI) of 26.14 kg/m^2, known with hypertension, previous stroke, chronic asthma, and allergic rhinitis diagnosed 7 years prior to his current presentation. The patient was under treatment with inhaled fluticasone/salmeterol 500/50 μg 2 times/day, salbutamol 100 μg, 2 inhalations as needed + tiotropium bromide 2,5 μg/dose, 2 inhalations/day in the morning, montelukast sodium 10 mg 1 tb/day, and intranasal beclomethasone twice daily. The patient presented 3 months prior to the current presentation with altered general state, dyspnea during light exertion, productive cough with mucous and muco-purulent sputum, and excessive sweating. The exacerbation was considered mild and was

treated at home with oral antibiotics and a short course of OCS. The prescribed medication had improved the general condition but there was a persistence of dyspnea and cough. During the next 2 months, the patient's condition changed, the dyspnea had worsened, became persistent at rest and was associated with nocturnal paroxysmal dyspnea, wheezing, low-grade fever and sweating, which led to the patient's admission to the Pulmonology Clinic. Given the frequent exacerbations, incomplete control of asthma under maximized treatment, and the existence of an increased number of blood eosinophils (3.7 • 10^3 elements/μL), initiation of benralizumab 30 mg/dose monthly treatment was prescribed, followed by subcutaneous administration every 8 weeks. The baseline ACT was 14 points, which implicitly suggested the lack of control of the disease. At only 2 hours after starting the treatment with benralizumab, the number of eosinophils decreased to 0.5 • 10^3 elements/μL. The patient had received the second and third dose at intervals of 1 month during which the general condition and dyspnea improved significantly, with no more nocturnal awakenings and the number of eosinophils remained low (0.01 • 10^3 elements /μL). The ACT questionnaire recorded 25 points after 2 months (3 doses).

Case no. 2

This is the case of a 67-year-old female patient, non-smoker, without exposure to respiratory toxins, with a 5 year history of persistent asthma, associated with ischemic heart disease with right bundle branch block and hypertension under treatment. The patient was prescribed inhaled budesonide/formoterol 320/9 μg (2 inhalations/day) and salbutamol 100 μg (2 inhalations as needed). Due to persistent symptoms (diurnal dyspnea, wheezing, nocturnal dyspnea in seizures) despite compliance with treatment and the correct technique of administration, the patient needed daily rescue medication with overuse of short-acting beta agonists (SABA) due to lack of disease control. The investigation of the contributing factors for the lack of disease control highlighted an allergic rhinitis for which treatment with mometasone furoate 2 × 2 nasal inhalations/day was initiated and exposure to air allergens, food allergens, animals, dust, chemicals were eliminated. Eight months prior, the patient presented to the Pulmonology Clinic with an altered general condition, dyspnea during low exertion, nocturnal wheezing, and cough with mucopurulent sputum. Due to the lack of asthma control with standard treatment (daily and nocturnal symptoms), exacerbation and decreased lung function (moderate obstructive ventilatory dysfunction), an ACT questionnaire of 12 points, an eosinophil count of 6.2 • 10^3 elements/μL, treatment with benralizumab 30 mg/dose was started with subcutaneous administration. Shortly after the first dose, the symptoms improved visibly with the decrease of cough, wheezing, and the need for SABA. The eosinophil count was 0.2 • 10^3 elements/μL after the first dose. The patient had received 6 doses of benralizumab, and during this period she did not show exacerbations, the nocturnal symptoms disappeared, the diurnal symptoms were minimal without the use rescue medication (less than 2 times/week), and the ACT score had increased up to 25 points.

Case no. 3

A 55-year-old hypertensive male patient, non-smoker, with a 3-year-old diagnosis of asthma on high dose fluticasone/salmeterol treatment 500/50 μg 2 times/day and SABA 100 μg 2 inhalations as needed, addressed to the Pneumology Clinic with exacerbated symptoms. The patient had had in fact an increase in the consumption of rescue medication (around 6 times/day) due to his persistent symptoms (dyspnea at low exertion, wheezing, irritating cough). Functional tests showed an average mixed ventilatory dysfunction and an ACT score of 14 points. The patient had a body mass index of 34 kg/m^2. Blood eosinophil count was 0.4 • 10^3 elements/μL, 6.5% of the total white blood cell count. Exacerbation management required short-term OCS, antibiotic therapy, education to optimize inhaled treatment and to eliminate contributing risk factors (antigen eviction, weight loss, proton pump inhibitors for gastro-esophageal reflux). Inhalation technique and treatment compliance were reevaluated and benralizumab was initiated. At 24 hours after the first dose of benralizumab, the symptoms had improved significantly and the patient did not require any use of rescue medication or OCS. The number of eosinophils had decreased to 0.01 • 10^3 elements/μL, 2.8% of all white blood cells.

Case no. 4

An 82-year-old patient (former 36 pack/year smoker with chronic obstructive pulmonary disease), known for associated persistent asthma for the last 4 years, with frequent infectious exacerbations, was admitted to the Pulmonology Clinic with dyspnea at low exertion, cough with mucopurulent sputum, chest pain, and wheezing. The chest computed tomography revealed advanced pulmonary emphysema but no other associated pathology. The cardiological work-up revealed signs of chronic pulmonary

heart disease in the early stages, and the respiratory functional tests showed a mixed reversible ventilatory dysfunction. The patient had undergone inhalator treatment with formoterol/budesonide 9/320 μg (2 inhalations/day), tiotropium bromide 2.5 μg/day and salbutamol 100 μg (2 inhalations as needed). The ACT questionnaire noted the existence of poor asthma control (12 points), the patient had a body mass index of 27.43 kg/m^2, and blood eosinophilia was increased (3.2 • 10^3 elements/μL). Along with the exacerbation treatment (antibiotics, oxygen, mucolytics), the initiation of biological treatment with benralizumab 30 mg subcutaneously was prescribed. Within 2 hours after the first dose, the number of eosinophils had decreased to 0.19 • 10^3 elements/μL and after 24 hours, the eosinophil count had decreased to 0.09 • 10^3 elements/μL. The clinical condition had significantly improved and the use of OCS was avoided. The ACT questionnaire at 2 months had improved significantly in parallel with consistent control of symptoms (decreased persistent dyspnea, nocturnal awakenings, increased daily physical activity, and the disappearance of nocturnal awakenings).

Table 1 illustrates the ACT questionnaire results of all 4 patients included in the present case series before the initiation of benralizumab, as well as after one month and 2 months, respectively. There was a clear increase in the ACT score in all patients.

DISCUSSIONS

The significant improvement in asthma control in the presented cases showed, on the one hand, the effectiveness, and on the other, the safety of benralizumab therapy after the acute phase of SEA exacerbation, thus indicating an effective and rapid response in symptom improvement and inflammation reduction. Blood eosinophil count had decreased significantly after the first dose (in 2 cases even after 2 hours) and symptoms had improved significantly, with reduced cough, sputum production, and dyspnea.

TABLE 1. The evolution of the ACT questionnaire values in the studied patients before and one to two months after benralizumab initiation

Case	ACT score before treatment	ACT score after 1 month of treatment	ACT score after 2 months of treatment
1	12	23	25
2	13	24	25
3	14	24	25
4	13	19	22

It is known that the inflammatory response in asthma is associated with increased eosinophils in the bronchial mucosa and blood, which increase additionally during exacerbations, thus leading to poor control of asthma.[9] In patients with SEA, there is an intense activation of T2-mediated inflammation, leading to an overexpression of IL-5 receptors which decreases the sensitivity of eosinophils to corticosteroids.[10]

The proapoptotic effect of corticosteroids on inflammatory cells decreases greatly if there is an antiapoptotic action caused by elevated levels of IL-5.[11] Thus, IL-5 is of crucial importance for the development and worsening of eosinophilic asthma associated with type 2 inflammatory immune response.[12,13]

The action of monoclonal antibodies, such as benralizumab, includes the blockade of IL-5 receptors in eosinophils and basophils, and the modulating effect of antibody-dependent cell-mediated cytotoxicity. This causes the total depletion of eosinophils in both blood and tissues. Benralizumab also decreases the concentrations of cytokines released by eosinophils (EDN and ECP).[14]

Numerous studies have shown that benralizumab decreases both current asthma symptoms and exacerbations in the first 30 days of treatment. The improvement occurs rapidly through IL-5 binding and decreased asthma-related inflammation.[4,5,8,15]

In the present proof of concept study, we used the Asthma Control Test (ACT) Questionnaire for the subjective assessment of asthma, before and after treatment with benralizumab. The analyzed criteria included the symptom levels within the last month, the frequency of rescue medication use, the effect of asthma on daily activities, and an overall assessment of the degree of asthma control.[16] All patients had poor control (score below 15) of asthma initially, despite maximized medication which included corticosteroids and long-acting beta-agonists. After initiating treatment (even after 1 dose), according to the ACT questionnaire all patients showed a significant improvement in symptoms and indirectly in the quality of life, with an associated decrease in SABA consumption. Starting from an initial score of 12–13 points, after 2 months, 3 of the patients obtained a score of 25 (maximum number of points) and 1 patient obtained a score of 22, which was explained by the existence of an overlap with smoking and COPD.

This strong impact on asthma control is due to the ability of benralizumab to drastically decrease eosinophils in the peripheral blood and the airways, thus restricting the entry of toxic proteins resulting from degranulation of eosinophils within the bronchial tissue.

CONCLUSIONS

The administration of monoclonal antibodies, such as benralizumab, in combination with pre-existing maintenance treatment that includes inhaled corticosteroids and long-acting beta-agonists, led to a rapid clinical improvement in all patients. This was shown by a lack of exacerbations, decreased symptoms, and overall improvement in the quality of life. The improvement was correlated with a decrease in the blood eosinophil count. In all patients, the treatment had a very good tolerance, without any side effects. The action of benralizumab was rapid in exacerbated patients, preventing the introduction of systemic corticosteroids. The ACT questionnaire was a useful tool for assessing the level of asthma control and was correlated with the evolution of blood eosinophil count. Benralizumab-type monoclonal antibodies should be integrated into clinical use in patients with incomplete asthma control despite optimal medical treatment. Further studies are required on larger patient sets.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Kommaraju K, Latifi M. Outpatient management of asthma in adults: A snapshot of the 2020 GINA report. Cleve Clin J Med. 2021;88:377-380.
2. Wang E, Wechsler ME, Tran TN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. Chest. 2020;157:790-804.
3. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. Int J Tuberc Lung Dis. 2015;19:10-20.
4. Menzies-Gow A, Corren J, Bel EH, et al. Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial. ERJ Open Res. 2019;5:00009-2019.
5. Park HS, Kim MK, Imai N, et al. Asian Benralizumab Study Group. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. Int Arch Allergy Immunol. 2016;169:135-145.
6. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol. 2013;132:1086-1096.
7. Bagnasco D, Heffler E, Testino E, Passalacqua G, Canonica GW. Pharmacokinetics and pharmacodynamics of monoclonal antibodies for asthma treatment. Expert Opin Drug Metab Toxicol. 2019;15:113-120.
8. Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017;33:1605-1613.
9. O'Quinn S, Xu X, Hirsch I. Daily patient-reported health status assessment improvements with benralizumab for patients with severe, uncontrolled eosinophilic asthma. J Asthma Allergy. 2019;12:21-33.
10. Dunican EM, Fahy JV. Asthma and corticosteroids: time for a more precise approach to treatment. Eur Respir J. 2017;49:1701167.
11. Pazdrak K, Moon Y, Straub C, Stafford S, Kurosky A. Eosinophil resistance to glucocorticoid- induced apoptosis is mediated by the transcription factor NFIL3. Apoptosis. 2016;21:421-431.
12. Molfino NA, Gossage D, Kolbeck R, Parker JM, Geba GP. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. Clin Exp Allergy. 2012;42:712-737.
13. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: Evidence and unmet needs. Curr Opin Allergy Clin Immunol. 2016;16:186-200.
14. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. Respir Med. 2016;111:21-29.
15. O'Quinn S, Xu X, Hirsch I. Daily patient-reported health status assessment improvements with benralizumab for patients with severe, uncontrolled eosinophilic asthma. J Asthma Allergy. 2019;12:21-33.
16. van Dijk BCP, Svedsater H, Heddini A, Nelsen L, Balradj JS, Alleman C. Relationship between the Asthma Control Test (ACT) and other outcomes: a targeted literature review. BMC Pulm Med. 2020;20:79.

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CASE REPORT

ANATOMY // SURGERY

Anatomical Variations of the Peroneus Tertius and Extensor Digitorum Longus Muscles – Case Presentation

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ABSTRACT

Introduction: The extensor digitorum longus and peroneus tertius muscles have multiple morphological variations. The tendinous slips of these muscles are used as grafts to replace other damaged tendons. **Case presentation:** We present a unique anatomical variant observed during dissection of a cadaver at the Department of Anatomy and Embryology of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania. The peroneus tertius muscle was identified on the left lower extremity as originating from the inferior third of the fibula and interosseus membrane. The posterior belly of this muscle joins the muscular belly of the extensor digitorum longus muscle. The tendons of toes II to V detach from the extensor digitorum longus muscle with an additional tendon. This last tendon gives off an accessory tendinous slip; lateral to this, the peroneus tertius muscle tendon is observed. In case of the right lower limb we also noted the peroneus tertius muscle originating from the distal part of the extensor digitorum longus muscle. Regarding the extensor digitorum longus muscle we describe an accessory tendinous slip. **Conclusion:** The anatomical variation reported in this study is similar to those reported by previous studies, but displays particular characteristics regarding the VI tendon of extensor digitorum longus and the joining of the peroneus tertius and extensor digitorum longus muscles in the left lower extremity.

Keywords: extensor digitorum longus muscle, peroneus tertius muscle, anatomical variations

INTRODUCTION

The anterior compartment of the leg is limited on one side by the osteofibrous plane of the medially placed tibia, the laterally placed fibula, and the interosseous membrane that attaches onto the interosseous crests of the diaphysis, and closes the interosseous space between the tibia and fibula; the other limiting structure is the anterior intermuscular septum that detaches from the crural fascia and inserts onto the anterior margin of the fibula and lateral margin of the tibia. The muscles of the anterior compartment of the

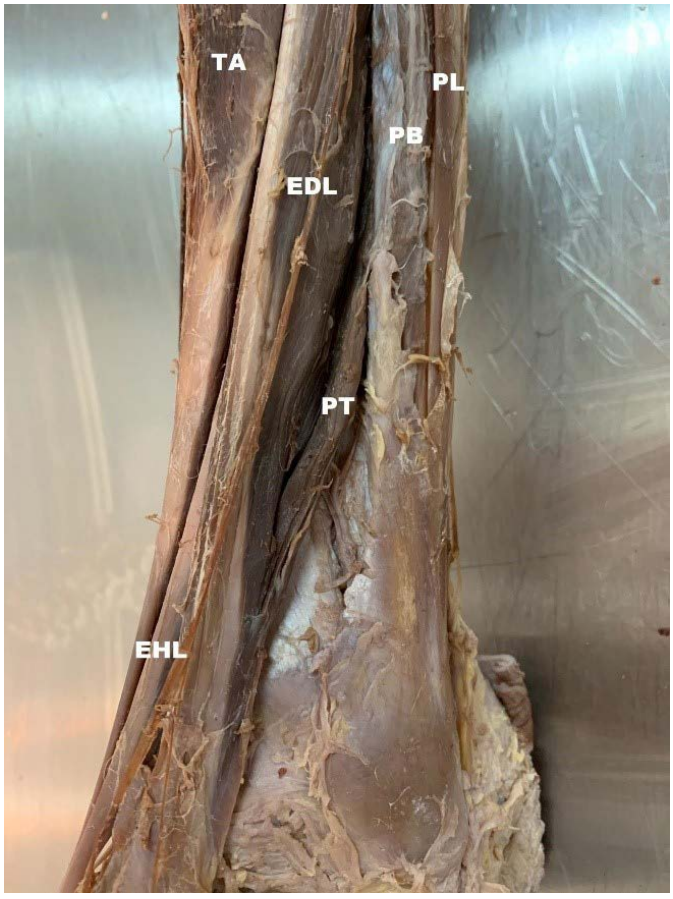

FIGURE 1. The muscle belly of the peroneus tertius muscle joins the muscle belly of the extensor digitorum longus muscle, left lower extremity. PT – musculus peroneus tertius; EDL – musculus extensor digitorum longus; EHL – tendon of musculus extensor hallucis longus; TA – musculus tibialis anterior; PB – musculus peroneus brevis; PL – musculus peroneus longus

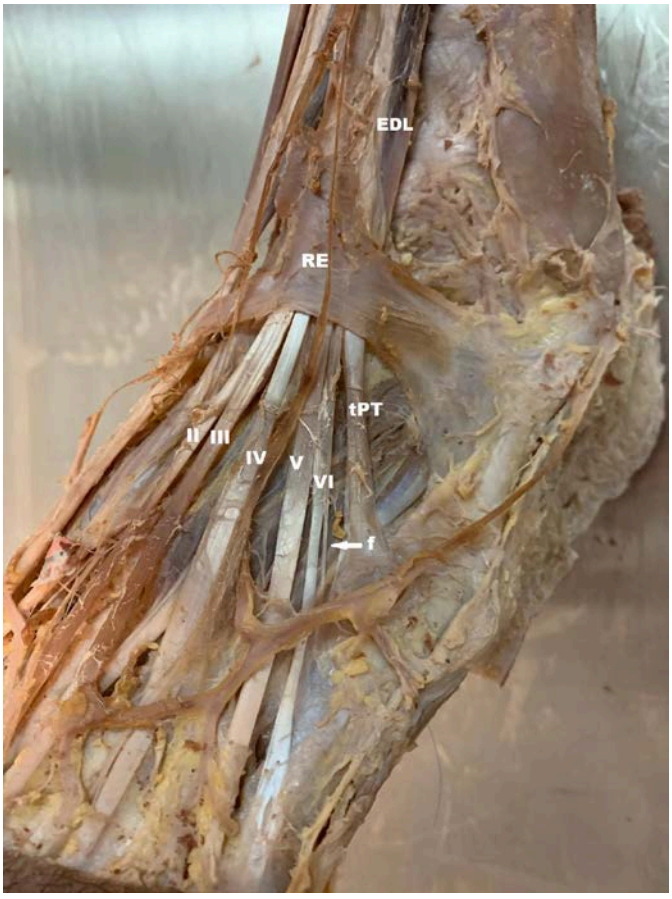

FIGURE 2. Tendon VI of EDL with its detached tendon slip (f), left lower extremity. RE – retinaculum extensorum, EDL – musculus extensor digitorum longus; tPT – tendon of musculus peroneus tertius

leg are listed in medio-lateral direction: musculus tibialis anterior (TA), musculus extensor hallucis longus (EHL), musculus extensor digitorum longus (EDL), and musculus peroneus tertius (PT). According to anatomy textbooks, TA comes from the lateral condyle and upper half of the lateral surface of the tibia, and the neighboring surface of the interosseous membrane and crural fascia; it inserts onto the plantar surface of the medial cuneiform. EHL originates from the middle part of the fibular medial surface and the neighboring interosseous membrane; it inserts onto the base of the distal phalanx of the halux through tendon I. EDL comes from the lateral condyle of the tibia, the proximal 2/3 of the anterior margin of the fibula, the superior part of the interosseous membrane, the deep fascia of the region and the anterior intermuscular septum; it inserts through fibrous expansions of tendons II–V onto the middle and distal phalanx of fingers II–V.[1,2]

EDL has the following topographical relationships on the leg: the anterior surface with the fascia of the leg and skin; medially with the tibialis anterior (TA) muscle and the extensor hallucis longus (EHL) muscle, as well as with the anterior tibial vasculo-nervous bundle; laterally through the anterior intermuscular septum with the peroneus longus (PL) and peroneus brevis (PB) muscles. EDL is innervated by branches of the deep fibular nerve. It produces extension of fingers II–V and dorsal flexion of the foot, with an additional external rotation (pronation).[2]

PT originates from the distal part of the fibula, the interosseus membrane, and anterior intermuscular septum; it inserts through a tendon (tendon VI) on the dorsomedial surface of the base of metatarsal V, and also the medial surface of this bone, through a thin expansion. It is often described as part of EDL.[3]

According to published data, the bellies and tendons of EDL and PT have numerous variations. Knowledge and identification of these variations is an advantage for orthopedic surgeons and plastic surgery surgeons; the addition-

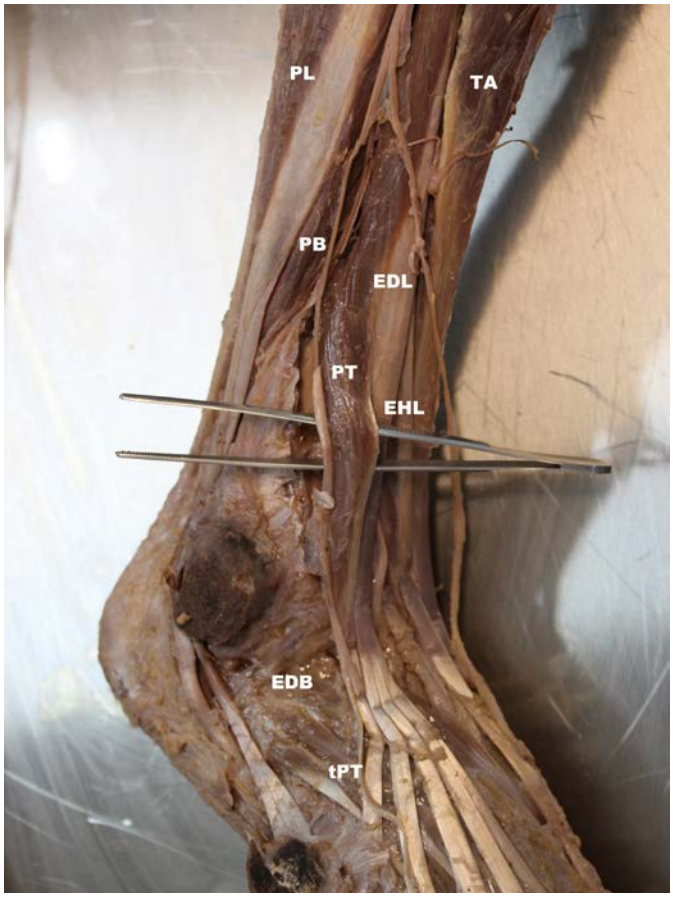

FIGURE 3. Separation of the PT muscle belly from EDL, right lower extremity. tPT – tendon of musculus peroneus tertius; PT – musculus peroneus tertius; tPT – tendon of musculus peroneus tertius; EDL – musculus extensor digitorum longus; ELH – tendon of musculus hallucis longus; EDB – musculus extensor digitorum brevis; TA – musculus tibialis anterior; PL – musculus peroneus longus; PB – musculus peroneus brevis

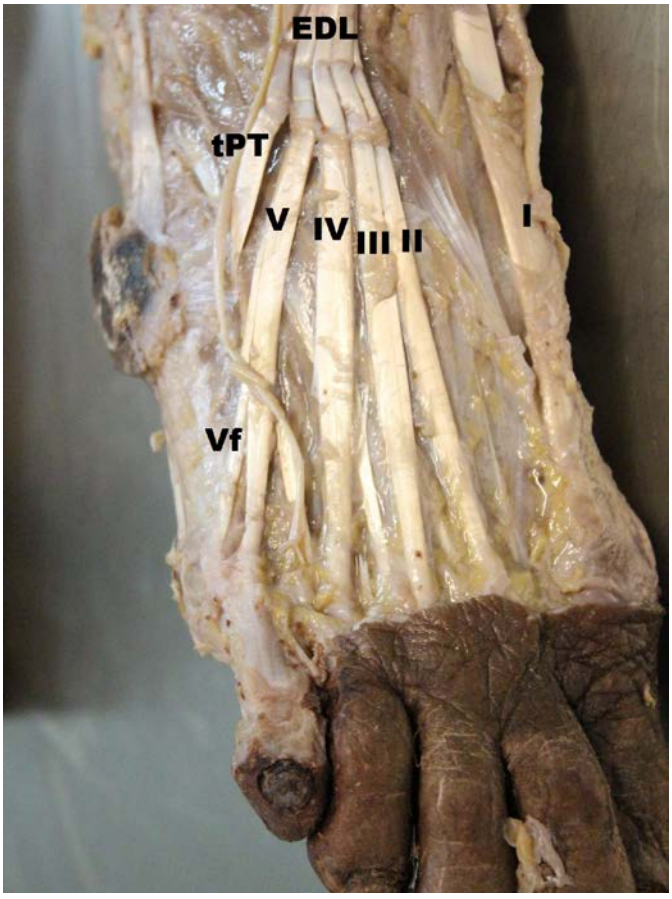

FIGURE 4. The tendon slip (Vf) detached from tendon V of EDL, right lower extremity. tPT – tendon of musculus peroneus tertius; EDL – tendon of musculus extensor digitorum longus; I – tendon of musculus extensor hallucis longus

al tendon slips are potential graft sources for replacement of damaged tendons.[4]

CASE PRESENTATION

Didactic dissection of a male cadaver has been performed at the Department of Anatomy and Embryology of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania, and multiple variations of the EDL and PT muscles have been identified.

On the left lower extremity, a muscle bundle has been identified as the PT muscle, originating from the inferior third of the fibula, the interosseous membrane, and the anterior intermuscular septum. After descending for about 10 cm, this bundle joins the muscle belly of the EDL muscle to create a common muscle body (Figure 1).

At the extensor retinaculum (RE) six tendons and a tendon slip detach from the common EDL (Figure 2). The first four tendons (II–V) correspond to the classical description of EDL tendons. Therefore, tendons II–V insert onto the middle and distal phalanx of the corresponding toes II to V. Tendon VI inserts onto the joint capsule of the 5th metatarsophalangeal joint, and the accessory tendon slip (f) detached from this tendon inserts onto the dorsal aponeurosis of the 5th toe. The tendon of the peroneus tertius muscle (tPT) inserts onto the dorsomedial surface of metatarsal V, according to the classical description (Figure 2).

On the right lower extremity, a PT muscle has been identified originating from the distal part of the EDL muscle belly, with a subsequent course that matches the one described in the literature. Its tendon (tPT) inserts onto the base of metatarsal V (Figure 3). EDL has four tendons (II–V) that insert onto the middle and distal phalanx of the corresponding toes II to V.[3] An accessory tendon slip (Vf)

detaches from tendon V and inserts of the joint capsule of the 5th metatarsophalangeal joint (Figure 4).

DISCUSSIONS

In this case study we describe an asymmetrical anatomical variation of the EDL and PT muscles. On the left lower extremity, we observed a muscle bundle identified as the PT muscle, originating from the inferior third of the fibula, the interosseous membrane and the anterior intermuscular septum. Following the descending course of this muscle bundle we observed that its muscle fibers join the muscular belly of the EDL muscle.

Therefore, this common muscle belly (EDL + PT) provided the following tendons in medio-lateral order: tendon II inserted onto the middle and distal phalanx of the 2nd toe, tendon III inserts onto the middle and distal phalanx of the 3rd toe, tendon IV inserted onto the middle and distal phalanx of the 4th toe, tendon V inserted onto the middle and distal phalanx of the 5th toe, tendon VI inserted onto the joint capsule of the 5th metatarsophalangeal joint, and the accessory tendon slip of this tendon (f) inserted onto the dorsal aponeurosis of the 5th toe, while tPT inserted onto the dorsomedial surface of the 5th metatarsal's base.

On the right lower extremity, we observed a PT muscle originating from the distal part of the EDL muscle belly. Its tendon (tPT) inserted onto the base of the 5th metatarsal, according to classical descriptions of insertion characteristics for PT. A tendon slip (Vf) detached from tendon V of the EDL muscle and inserted onto the capsule of the 5th metatarsophalangeal joint. Insertion of the remaining tendons (II–V) was identical to that observed on the left lower extremity.

Several anatomical variations of the EDL muscle insertion have been reported.[5–7,10,11] Just like in our case, numerous bifurcation variations and additional tendon slips are discussed. In these cases, the bifurcated tendons and tendon slips insert onto their corresponding toes. In our case, we observed on the right lower extremity the bifurcated insertion of tendon V, along with an accessory tendon slip (Vf) that also inserted onto the 5th toe.[7,8] More precisely, this accessory tendon slip inserted onto the joint capsule of the 5th metatarsophalangeal joint. Berman *et al.* reported accessory tendon slips inserting onto the metatarsals that correspond to the classical tendons (II–V), onto the EDL tendons or onto the dorsal aponeurosis of the fingers.[7] There have been case reports where EDL tendons of one or more toes were missing or an additional tendon was described. Apart from these findings, in our case, we observed an additional tendon (VI) on the left lower extremity, which inserted onto the joint capsule of the metatarsophalangeal joint of the 5th toe. This additional tendon presented a tendon slip (f) inserting on the dorsal aponeurosis of the 5th toe, which has not been reported so far. No similar variants were found in the literature.

In some cases, enlargement of PT has been reported, and if this was missing, then compensatory hypertrophy of the EDL muscle may have been present.[9–14]

PT may be present in over 90% of the cases, but recent studies suggest a lower prevalence (49.1–81.5%). The PT muscle is characteristic to humans; it may have different sizes and plays a role in bipedal movements.[15–17]

Only a small number of studies deal with anatomical variations of the PT muscle. Rourke *et al.* described a particular variation of the PT muscle, originating as a continuation of the EDL muscle, similar to the right lower extremity of our case. An interesting aspect of this study was the asymmetry between the PT muscles of the same cadaver.[18] PT muscle asymmetry was also present in our case.

The left lower extremity has the most frequent variants of the PT muscle,[3] with proper origin and classical insertion, but the particular aspect of our case was the joining of the PT and ELD muscle bellies. This variation was presented in only one previously reported case.[19] The right lower extremity presented a more rare variant, which has already been reported by other authors,[3,6] originating from the distal part of the EDL muscle belly, but with classical course and insertion.

Yildiz *et al.* have described a unique variation. The EHL muscle belly bifurcated at 17 cm from its origin into a lateral and a medial muscle bundle. The lateral muscle bundle inserted onto the base of the 5th metatarsal and has been identified by the authors as the PT muscle.[20] Apart from the variation described earlier, we did not find variations of the EHL in both lower extremities, nor variations of the EHL which interfere with the EDL or PT muscles.

The most particular findings in our study on the left lower extremity, were the 6th tendon of the EDL and its accessory tendinous slip, along with the joining of the PT and EDL muscle bellies. Other least common findings described by other authors include the bifurcation of the 5th tendon of EDL and the origin of PT from the distal half of EDLs' muscle belly on the right lower extremity.[18,20]

Numerous studies have emphasized the importance of the PT muscle in medical practice, especially in plastic surgery, considering its frequent use as a graft (island flap). It has good viability due to numerous anastomoses of perforating branches of the fibular, malleolar and lateral tarsal arteries.[21]

CONCLUSIONS

Anatomical variations of shape, origin and insertion of musculus extensor digitorum longus and peroneus tertius have been reported in publications with clinical implications in the field of orthopedic surgery and plastic surgery. The particular aspect of our case, which has not yet been reported, was the fact that the muscle belly of musculus peroneus tertius joined up with the belly of musculus extensor digitorum longus.

CONFLICT OF INTEREST

Nothing to declare.

ETHICAL CONSIDERATIONS

The case presentation and the use of cadavers for scientific purposes was approved by the Ethics Committee of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania (1323/04.2021).

REFERENCES

1. Seres-Sturm L, Pávai Z, Seres-Sturm M, Dénes L. A végtagok anatómiája. Târgu Mureş: University Press, 2005; p. 177-178.
2. Enciulescu C. Anatomia Membrelor. Târgu Mureş: University Press, 2015; p. 82-83.
3. Gray H, Carter HV. Grays Anatomy. London: Arcturus, 2019; p. 1406-1408.
4. Ramirez D, Gajardo C, Caballero P. Clinical Evaluation of Fibularis Tertius Muscle Prevalence. *Int J Morphol*. 2010;28:759-764.
5. Shigematsu M, Tsubakihara M, Maruyama S. On the m. extensor digitorum longus. *Kurume Igakkai Zasshi*. 1956;19:1297-1302.
6. Bhadkamkar AR, Mysorekar VR. Anomalous peroneus tertius and extensor digitorum longus muscles. *J Anat Soc India*. 1961;10:37-38.
7. Kelikian AS, Sarrafian SK. Sarrafian's Anatomy of the Foot and Ankle. Lippincott Williams and Wilkins, 2011; p. 122-130.
8. Stevens K, Platt A, Ellis H. A cadaveric study of the peroneus tertius muscle. *Clin Anat*. 1993;6:106-110.
9. Chaney D, Lee M, Khan M. Study of ten anatomical variants of the foot and ankle. *J Am Podiat Med Assn*. 1996;86:532-537.
10. Plochocki JH, Bodeen M. Unusual supernumerary muscle in the anterior compartment of the leg. *Clin Anat*. 2010;23:104-105.
11. Banerje A, Singh S, Raza K. Unilateral Variation in Extensor digitorum longus muscle. *Clin Ter*. 2016;167:150-151.
12. Witvrouw E, Borre KV, Willems TM. The Significance of Peroneus Tertius Muscle in Ankle Injuries. *Am J Sports Med*. 2006;34:1159-1163.
13. Jungers WL, Medlrum D, Stern JT. The functional and evolutionary significance of the human peroneus tertius muscle. *J Hum Evol*. 1993;25:377-386.
14. Krammer EB, Lischka MF, Gruber H. Gross anatomy and evolutionary significance of the human peroneus III. *Anat Embryol*. 1979;155:291-302.
15. Stevens K, Platt A, Ellis H. A cadaveric study of the peroneus tertius muscle. *Clin Anat*. 1993;6:106-110.
16. Chaney D, Lee M, Khan M. Study of ten anatomical variants of the foot and ankle. *J Am Podiatr Med Assoc*. 1996;86:532-537.
17. Joshi S, Joshi S, Athavale S. Morphology of peroneus tertius muscle. *Clin Anat*. 2006;19:611-614.
18. Rourke K, Dafydd H, Parkin I. Fibularis tertius: Revisiting the anatomy. *Clin Anat*. 2007;20:946-949.
19. Kaur AA, Poonam V, Sudhir A. Evaluation of the Origin and Insertion of Extensor Digitorum Longus: Clinical Correlation and Literature Review. *JRMEE*. 2011;1:50-53.
20. Yildiz S, Yalcin B. An unique variation of the peroneus tertius muscle. *Surg Radiol Anat*. 2012;34:661-663.
21. Bertelli J, Khoury Z. The peroneus tertius island muscle flap (23.3.91). *Surg Radiol Anat*. 1991;13:243-244.

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CASE REPORT

OPHTALMOLOGY // RADIOLOGY

Uveal Tumor with Retinal Detachment – Case Report of a Rare Malignancy

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ABSTRACT

Introduction: Melanoma, a type of tumor originating from melanocytes, can have different anatomic locations. Ocular melanoma represents about 5% of total melanomas and is a rare condition, with an overall incidence rate of 5.1 cases/million/year. The most frequent location of uveal melanoma is the choroid (90%), followed by the ciliary body (6%) and the iris (4%). The most frequent symptoms of choroidal melanoma are blurred vision and photopsia. The therapeutic approach of uveal melanoma can be classified into two main categories: globe preservation treatments and enucleation. **Case presentation:** We present the case of a male patient diagnosed at the age of 72 years with right choroidal melanoma, who had a preexisting condition of visual impairment due to the presence of right mature cataract. The diagnosis was delayed in the course of the disease, as retinal detachment had already been installed. The patient was treated with local radiotherapy. **Conclusion:** Uveal melanoma is a malignancy in which a novel therapeutic approach, including magnetic resonance imaging is needed in order to improve the outcome of these patients, preserve vision and prevent systemic extension of the disease.

Keywords: uveal tumor, choroid melanoma, retinal detachment, radiotherapy, magnetic resonance imaging

INTRODUCTION

Melanoma, a type of tumor originating from melanocytes, can have various anatomic locations including the skin, mucous membranes, and the ocular region. The eye origin of melanoma represents about 5% of total melanomas, with 83% of them being located in the uveal region, 5 % in the conjunctiva, and 10% in other ocular sites.[1]

Uveal melanoma is a rare condition, with an overall incidence of 5.1 cases/million/year, according to an analysis conducted by the United States National Cancer Institute over a 36-year period,[2] and of 1.3–8.6 cases/million/year, according to a European Cancer Registry-based study.[3]

This condition is diagnosed more frequently in the elderly, with a peak incidence rate at 70 years, being rarely discovered in children.[1] Men are considered

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to be more affected than women, and Caucasians have a higher incidence rate than African Americans, with a ratio ranging from 1:15 to 1:50, according to different studies.[4–6] Regarding location, the tumor is most frequently located in the choroid (90%), followed by the ciliary body (6%) and the iris (4%).[7]

Risk factors for developing uveal melanoma can be divided into two main categories: those related to the patient, and environmental factors.

Patient-related factors include:

1. *hair, skin color, and tan ability* (blond hair, fair skin, and difficulty to tan), which are considered to be risk factors for developing melanoma;[8]
2. *choroidal, iris, and cutaneous nevus* – increases the risk to develop ocular melanoma up to 4.36 to 10.4 times;[1]
3. *oculodermal melanocytes* – a congenital pigmentary abnormality that leads to slate-grey pigmentation of the uvea, sclera, orbit, meninges, palate, tympanic membrane, and periocular skin, which substantially increases the risk to develop uveal melanoma. It is usually unilateral and is linked to a lifetime risk of uveal melanoma.[9,10]

Environment-related factors include:

1. *sunlight exposure* – there is no general agreement on the correlation between direct exposure to sunlight and the risk of developing melanoma, and studies show contradictory results.[11]
2. *intermittent exposure to artificial ultraviolet light* – there is no clear proof regarding ultraviolet light exposure from occupational activities being an independent risk factor for uveal melanoma.[12]

Clinical symptoms depend on the anatomical location of uveal melanoma. The symptoms of choroidal or ciliary body melanoma include blurry vision (38%), photopsia (9%), floaters (7%), loss of visual field (6%), visible tumor (3%), and pain (2%); up to 30% of patients may be asymptomatic. Choroidal melanoma rarely presents in a diffuse manner (6%), being usually a dome-shaped mass (75%), pigmented in about 55% of cases, non-pigmented in about 15%, and mixed in about 30% of cases. This type of uveal melanoma is associated with intraocular hemorrhage and with retinal detachment (71%).[1]

Iris melanoma is usually diagnosed at a younger age than choroidal or ciliary body melanomas and can be circumscribed (90%) or diffuse (10%). It is associated with heterochromia (change of iris color), corectopia (pupil distortion) or secondary glaucoma due to compression or invasion of the anterior chamber angle, leading to outflow obstruction.[1] It has a better prognosis than ciliary body or choroidal melanomas, with 5 to 10 times lower mortality rates.[7]

Gonioscopy, fundus examination, conventional ultrasonography, anterior-segment optical coherence tomography (AS-OCT), magnetic resonance imaging (MRI), ultrasound biomicroscopy (UBM), and fine-needle aspiration biopsy, are all tools used to diagnose uveal tumors.[1]

The differential diagnosis of uveal melanoma is complex and depends on its anatomical location. Choroidal or ciliary body melanomas must be differentiated from choroidal nevus, congenital hypertrophy of retinal pigment epithelium, circumscribed choroidal hemangioma, or age-related macular degeneration.[1] Circumscribed iris melanomas must be differentiated from iris nevus, leiomyoma, iris cyst, metastasis, and inflammatory conditions, whereas diffuse iris melanomas must be differentiated from pigmentary glaucoma, hemosiderosis, melanocytomalytic glaucoma, or congenital heterochromia.[1]

The treatment of uveal melanoma depends on several factors: type and location of the tumoral process, tumor size and extension, visual acuity at diagnosis, and the presence or absence of systemic involvement.

The therapeutic approach can be classified into two main categories: globe preservation treatments (radiotherapy, laser therapy, surgery) and enucleation. There are different modalities of radiotherapy (photon-based external-beam radiation, brachytherapy) with excellent results regarding local control of the tumor and globe preservation, but with associated long-term vision loss.[13] The most frequent complications associated with radiotherapy are radiation-induced retinopathy (45–67%), neovascular glaucoma (28.3%), cataract (44%), and macular edema (24.5%). As far as surgical therapy is concerned, enucleation is the most common surgical approach for patients with large tumoral size, extensive extraocular growth, circumferential tumor invasion, and vision loss.[1]

CASE PRESENTATION

We present the case of a male patient, aged 72, who was referred to the ophthalmologist due to vision problems and was diagnosed with mature cataract of the right eye and incipient cataract of the left one. The ocular fundus examination revealed left retinal angiosclerosis, while the right eye fundus could not be properly appreciated. The patient was sent to surgery and right intracapsular cataract extraction was performed. During surgery, the ophthal-

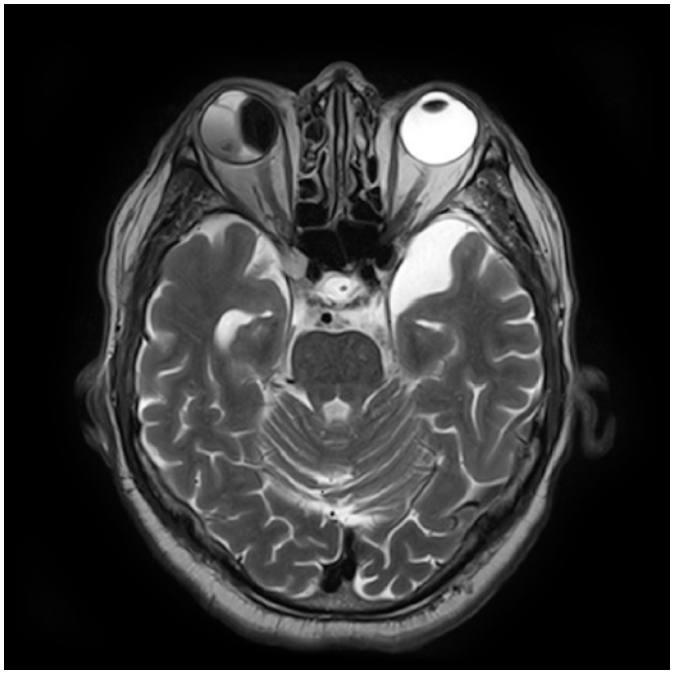

FIGURE 1. Axial MRI T2 – right hypointense subretinal mass lesion associated with retinal detachment

mologist noticed a hyperchrome mass in the nasal region of the right eye, with apparent intravitreal extension and vascularization of the pupillary area. Craniocerebral MRI was indicated for proper evaluation of the case.

MRI examination of the brain and orbits revealed the presence of an expansive process of 19 × 12 × 21 mm in the medial portion of the right eye, located in the uveal tract, more precisely at the choroidal level, with associated right retinal detachment (Figure 1). The described lesion presented T1 and T2 hyposignal and intense contrast enhancement, the MRI aspect being suggestive for increased melanin concentration at this level, and led to the diagnosis of uveal melanoma, located in the right choroidal region (Figure 2).

Severe cerebral atrophy with associated vascular lacunes and periventricular leukoaraiosis, left temporal arachnoid cyst, right frontal subcutaneous lipoma, frontal and ethmoidal sinusitis, and bilateral mastoiditis completed the imaging report.

The patient was treated with local radiotherapy in order to preserve his ocular globe and will be further monitored, both clinically and using imaging methods, for early detection of any additional visual impairment or systemic dissemination of the melanoma.

DISCUSSION

Uveal melanoma is a rare malignancy, the median age at diagnosis is 62 years with a peak of incidence between 70 and 79 years, and men are more frequently diagnosed with this pathology.[13]

Early diagnosis, although achieved in numerous cases, is

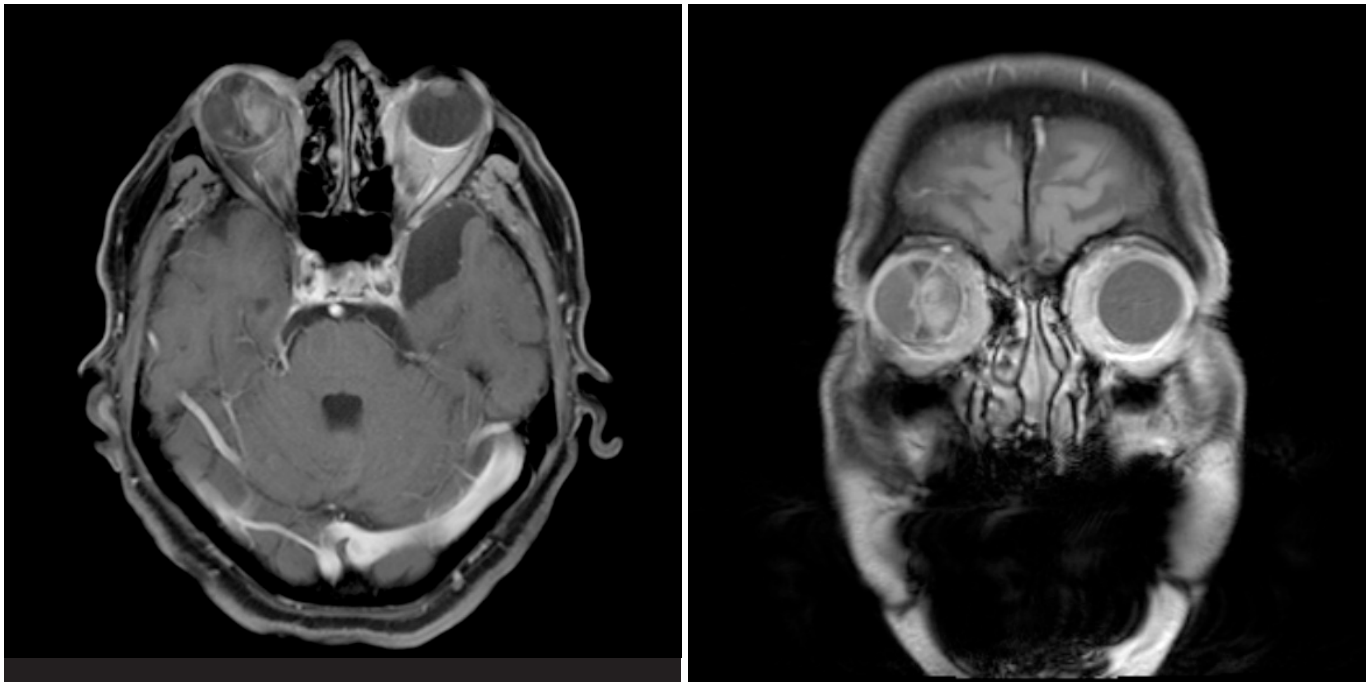

FIGURE 2. MRI T1 contrast enhanced axial (**A**) and coronal (**B**) – right subretinal mass lesion enhancing contrast with characteristic hyperintense signal

not sufficient for a good prognosis of these patients due to associated visual morbidity and metastatic dissemination. The appearance of metastases leads to a median survival of only 6–12 months, better for those patients who received treatment for metastasis than for those who did not.[13]

External beam radiation therapy performed pre-enucleation is not recommended, as its use did not show any certain benefits. In cases of patients who refuse enucleation as a therapeutic approach, there are other solutions, like transscleral or transretinal resection, which are, however, surgeon- and site-dependent and cannot be performed everywhere. Although they preserve the globe and the patient's vision, these techniques are associated with important complications including retinal detachment (21%), ocular hypertension (21%), and submacular hemorrhage (16%).[13]

One of the most important topics to consider is that although current treatment options achieve local control in a great number of cases, they are frequently associated with vision loss and systemic metastases. Therefore, novel therapeutic approaches are needed. Several studies concluded that systemic adjuvant therapy may prevent the appearance of metastases to some extent but has little effect on improving outcomes.

Innovative therapeutic strategies, such as heparin sulfate proteoglycans, are currently being developed. Gene expression and epigenetic modifying agents like DNA methyltransferase inhibitors will be studied in future studies.[13] High expression of insulin growth factor receptor 1 (IGF-1R) is associated with lower survival rates. This association is thought to be explained by the liver production of IGF-1, the liver being also the most affected organ by metastatic spreading. According to this finding, it is thought that the blockage of IGF-1R may be a future therapeutic approach of uveal melanoma. Further studies are needed in order to fully understand these topics.[14]

Optimal post local treatment follow-up is still under research. It is considered that MRI examination performed twice a year has greater predictive value for detecting metastases than other imaging techniques (abdominal ultrasonography, computed tomography scans, or positron-emission tomography imaging) and is also radiation-free.[15]

We presented the case of a male patient diagnosed at the age of 72 years with a right uveal melanoma, located at the choroid level. This pathology had developed in a patient with a preexisting condition of visual impairment due to mature cataract. This had led to a delayed diagnosis which allowed the development of the tumoral process, as retinal detachment was already installed. This case raises awareness on the importance of periodic ophthalmological examination in the elderly population, as it is the most affected group by tumoral processes of the uveal region. Complex imaging techniques are needed for a proper diagnosis and monitoring of this disease, with its local and systemic involvement.

CONCLUSIONS

Uveal melanoma is a malignancy in which novel therapeutic approaches are needed in order to improve the outcome of these patients, to preserve vision, and to prevent systemic extension of the disease. More research is necessary in order to find the best therapeutic approach for this type of rare malignancy.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Kaliki, S, Shields, C. Uveal melanoma: relatively rare but deadly cancer. *Eye*. 2017;31:241-257.
2. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118:1881-1885.
3. Virgili G, Gatta G, Ciccolallo L, et al. Incidence of uveal melanoma in Europe. *Ophthalmology*. 2007;114:2309-2315.
4. Shields CL, Kaliki S, Cohen MN, et al. Prognosis of uveal melanoma based on race in 8100 patients: The 2015 Doyne Lecture. *Eye (Lond)*. 2015;29:1027-1035.
5. Margo CE, Mulla Z, Billiris K. Incidence of surgically treated uveal melanoma by race and ethnicity. *Ophthalmology*. 1998;105:1087-1090.
6. Hu DN, Yu GP, McCormick SA, et al. Population-based incidence of uveal melanoma in various races and ethnic groups. *Am J Ophthalmol*. 2005;140:612-617.
7. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol*. 2009;127:989-998.
8. Weis E, Shah CP, Lajous M, et al. The association between host susceptibility factors and uveal melanoma: a meta-analysis. *Arch Ophthalmol*. 2006;124:54-60.
9. Singh AD, De Potter P, Fijal BA, et al. Lifetime prevalence of uveal melanoma in white patients with oculo(dermal) melanocytosis. *Ophthalmology*. 1998;105:195-198.
10. Shields CL, Kaliki S, Livesey M, et al. Association of ocular and oculodermal melanocytosis with the rate of uveal melanoma metastasis: analysis of 7872 consecutive eyes. *JAMA Ophthalmol*. 2013;131:993-1003.
11. Shah CP, Weis E, Lajous M, et al. Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. *Ophthalmology*. 2005;112:1599-1607.
12. Ge YR, Tian N, Lu Y, et al. Occupational cooking and risk of uveal melanoma: a meta-analysis. *Asian Pac J Cancer Prev*. 2012;13:4927-4930.
13. Krantz BA, Dave N, Komatsubara KM, et al. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clinical ophthalmology (Auckland, N.Z.)*. 2017;11:279-289.
14. Kaliki S, Shields C, Shields J, et al. Uveal melanoma. *Indian Journal of Ophthalmology*. 2015;63(2):93-102.
15. Rose AM, Luthert PJ, Jayasena CN, et al. Primary orbital melanoma: presentation, treatment, and long-term outcomes for 13 patients. *Front Oncol*. 2017;7:316.

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CASE REPORT

VASCULAR SURGERY // INTERNAL MEDICINE

A Rare Case of Abdominal Aortic Aneurysm with Ureteral Compression

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ABSTRACT

Introduction: In this report, we present a rare case of aortic aneurysm with associated left ureter obstruction and consequent hydronephrosis. **Case presentation:** A 62-year-old man was admitted for epigastric and periumbilical pain, extended in the spine, and anuria. As for associated diseases, he presented arterial hypertension stage II/III, chronic ischemic cardiomyopathy, acidosis, hyperpotassemia, spondylosis with radiculopathy, acute renal failure, renal lithiasis, and eating difficulties. After performing a CT scan, the patient was diagnosed with giant abdominal infrarenal aortic aneurysm with ureter compression, and retroperitoneal rupture with common and internal iliac arteries occlusion. We performed a xifo-pubian laparotomy with endoaneurysmorrhaphy and aortoiliac bilateral bypass using silver Dacron vascular prosthesis (16 × 8 mm in diameter). Douglas drainage was necessary, ending with laparoraphy. The patient presented a favorable postoperative evolution. **Conclusion:** Open surgery remains the gold standard method of treatment for large aortic aneurysms, given the inability of endovascular procedures to solve problems caused by compression.

Keywords: laparotomy, ureteral compression, Douglas drainage, laparoraphy, abdominal aortic aneurysm

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a vascular disorder of multifactorial origin, with a high fatality rate. AAA represents a significant challenge for the surgeon because of the extensive periaortic inflammation, and retroperitoneal and perianeurysmal fibrosis, which can compromise the structure of the urinary tract.

Progressive expansion, compression of the visceral organs, rupture, but also embolization and thrombosis are the main characteristics of an AAA.[1] In developed countries, AAA represents 1–3% of the incidence of mortality concerning men aged 65–85 years. It is more common in men, but it seems that female patients have a higher risk of rupture and worse prognosis.[2] Risk factors for the development of AAA include atherosclerosis, cerebrovascular disease, coronary

artery disease, first-degree relative with AAA, history of other vascular aneurysms, hypercholesterolemia, hypertension, male gender, obesity, older age, and tobacco use.

Patients are usually complaining about back pain and abdominal pain, but sometimes the AAA is asymptomatic until the rupture occurs, which can be a real catastrophe. Patient monitoring, using abdominal ultrasound, computed tomography (CT) angiography, and magnetic resonance (MR) angiography, plays an important role in attenuation of the rupture risk and also provides an accurate measurement of the aneurysm size.[3] AAA with ureteral obstruction occurs in 35% of patients with obstructive uropathy.[4] Compared to open surgical repair, endovascular interventions are preferred in AAA due to the low mortality and morbidity. Dissection and vascular control are challenging in the open surgical intervention, and there is also a significant risk of accidental injury of the surrounding visceral structures such as the ureters, left renal vein, inferior vena cava, duodenum, and sigmoid colon.[5]

CASE PRESENTATION

We present the case of a 62-year-old man, who at first presented to the emergency department of a territorial hospital, complaining of pain in the epigastric and umbilical regions, accompanied by anuria and extension of the pain in the back. The complaints started suddenly, 48 hours before. After CT imaging, the patient was diagnosed with giant abdominal aortic aneurysm with ureteral compression (Figure 1). He was transferred to a tertiary care hospital, the Vascular Surgery Clinic of the Emergency Clinical County Hospital of Târgu Mureș, Romania. As comorbidities, he had arterial hypertension stage II/III, chronic ischemic cardiomyopathy, acidosis, hyperpotassemia, spondylosis with radiculopathy, acute renal failure, renal lithiasis, and eating difficulties. The patient went into surgery, at the beginning of which a small/medium amount of ascites was found in the abdominal cavity, without blood in the peritoneum. We exposed the giant pulsatile tumoral mass and prepared the abdominal aorta and the iliac arteries bilaterally (Figure 2). The left common iliac artery and the left internal iliac artery were aneurysmal and thrombosed, without pulsation. Systemic heparinization, 2500 Ivo in bolus was given before clamping the subrenal aorta and iliac arteries. A longitudinal incision was performed along the aneurysm until the healthy aorta wall, and extended to the aortic bifurcation. Intraluminal thrombosis was discovered together with a thick aortic wall (3 cm), injury/rupture of the posterior aortic wall (ca. 5 × 5 cm) above the spine, and the presence of retrograde blood flow from the right common iliac artery. A T-T proximal anastomosis at subrenal aortic level was performed using a 4.0 surgi-pro wire. A silver Dacron bifurcated vascular prosthesis (16 × 8 mm diameter) was inserted (Figure 3). The branches of the prosthesis were clamped to the proximal anastomosis, and the body was clamped again. Next, we performed a bilateral aortoiliac tunneling. On the left side we also performed a T-T anastomosis with a 4.0 surgical wire, with the ligature of the proximal arterial branch. On the right side a T-L anastomosis was performed using 4.0 surgical wire. The aorta was unclamped, the hemostasis was managed, and the aneurysmal sac was sutured over the vascular prosthesis. The patient agreed to the pub-

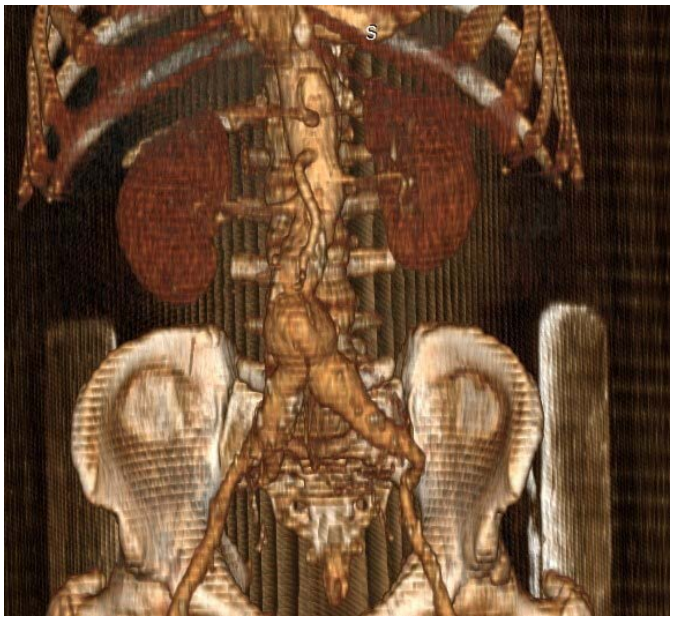

FIGURE 1. Abdominal aortic aneurysm with ureteral compression

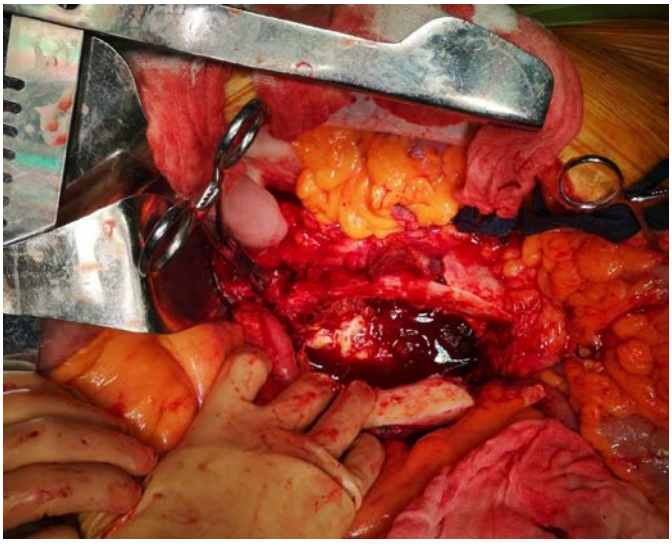

FIGURE 2. Infrarenal aortic aneurysm

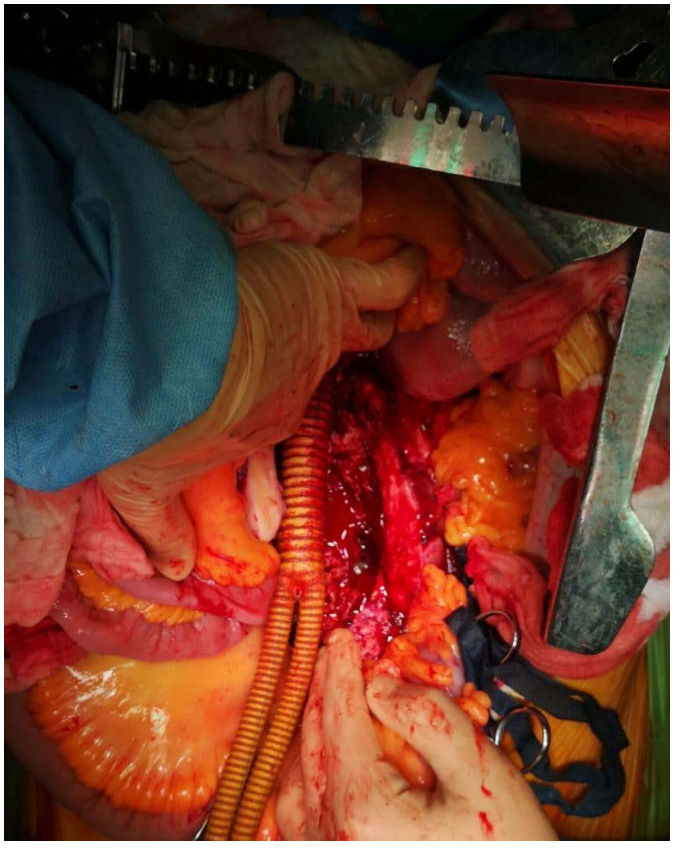

FIGURE 3. Silver Dacron bifurcated vascular prosthesis

lication of his data and the institution where the patient had been admitted, approved the publication of the case.

DISCUSSIONS

Besides pharmacological treatment, there are two common types of surgical treatment for AAA: endovascular (interventional placement of a stent graft) and open repair (vascular graft via laparotomy). Selection of the type of repair is strictly individualized, depending on age, anatomy, and comorbidities. In a German clinical research (practice guideline published) in 2018, the majority of patients received endovascular treatment (EVAR), and only those with a lower morbidity rate benefited from open surgery. As a result, the 30-day mortality rate was lower in patients with EVAR (1.16%), compared to those with open repair (3.27%). The study concluded that endovascular treatment offers a higher degree of safety and is more preferred for patients with asymptomatic AAA.[6]

Open AAA repair can have several major complications such as myocardial infarction, pulmonary edema, cardiac arrhythmia, and acute renal failure. Elderly patients and smokers have a higher risk of major complications. In a retrospective cohort study, the authors analyzed the correlation between fluid balance and complications in 100 consecutive patients. Patients with complications had greater cumulative positive fluid balance after surgery, from $p < 0.01$ on day 0 to $p < 0.04$ on day 3. Moreover, they had significantly longer stays in the intensive care unit and in the hospital.[7]

Besides complications that occur during the AAA repair, there are also graft-related complications. In a study that included 307 patients who underwent AAA repair between 1957 and 1990 at the Mayo Clinic and two affiliated hospitals, 29 patients had graft-related complications. The most common complication was anastomotic pseudoaneurysm (3%), followed by graft thrombosis, graft infection, graft-enteric erosion/fistula, colon ischemia, and atheroembolism.[8]

Another factor that impacts recovery after an AAA repair is gender. According to a population-based survey in Sweden, patients with ruptured AAA showed significant differences in recovery between women and men, and female patients presented a greater risk of death in case of a symptomatic aneurysm (81.1% for women and 68.5% for men).[6]

CONCLUSIONS

Open surgery remains the gold standard method of treatment for large aortic aneurysm, given the inability of endovascular procedures to solve problems caused by compression.

CONFLICT OF INTEREST

Nothing to disclose.

REFERENCES

1. Legg JS, Legg LM. Abdominal Aortic Aneurysms. *Radiol Technol*. 2016;88:145-163.
2. Ullery BW, Hallett RL, Fleischmann D. Epidemiology and contemporary management of abdominal aortic aneurysms. *Abdom Radiol*. 2018;43:1032-1043.
3. Aggarwal S, Qamar A, Sharma V, Sharma A. Abdominal aortic aneurysm: A comprehensive review. *Exp Clin Cardiol*. 2011;16:11-15.
4. von Fritschen U, Malzfeld E, Clasen A, Kortmann H. Inflammatory abdominal aortic aneurysm: A postoperative course of retroperitoneal fibrosis. *Journal of Vascular Surgery*. 1999;30:1090-1098.
5. Wilt TJ, Lederle FA, Macdonald R, Jonk YC, Rector TS, Kane RL. Comparison of endovascular and open surgical repairs for abdominal aortic aneurysm. *Evid Rep Technol Assess (Full Rep)*. 2006;144:1-113.
6. Schmitz-Rixen T, Böckler D, Vogl TJ, Grundmann RT. Endovascular and Open Repair of Abdominal Aortic Aneurysm. *Dtsch Arztebl Int*. 2020;117:813-819.
7. McArdle GT, Price G, Lewis A, et al. Positive Fluid Balance is Associated with Complications after Elective Open Infrarenal Abdominal Aortic Aneurysm Repair. *European Journal of Vascular and Endovascular Surgery*. 2007;34:522-527.
8. Hallett JW, Marshall DM, Petterson TM, et al. Graft-related complications after abdominal aortic aneurysm repair: Reassurance from a 36-year population-based experience. *Journal of Vascular Surgery*. 1997;25:277-286.

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IMAGE FOCUS

DERMATOLOGY // EPIDEMIOLOGY

The Ugly Face of Face Masks

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ABSTRACT

Introduction: Prolonged and tightly use of face masks has been identified as cause for skin damage during the COVID-19 pandemic. **Case series presentation:** We evaluated patients seen in the outpatient clinic between March and May 2020, during the lockdown period, focusing on skin damage related to the use of face masks. We aimed to highlight the major impact of routine usage of face masks on the skin of individuals of different ages and professions. Contact dermatitis was prevalent, but we also recorded many cases of outbreak of seborrheic dermatitis, acne, rosacea, perioral dermatitis, atopic dermatitis, folliculitis, as well as neurotic excoriations caused by anxiety, tinea, and impetigo. We also observed a delay in the diagnosis of benign and malignant tumors. **Conclusions:** The most important step should be the assessment of dermatologic pathology related to the use of face masks. They say a picture is worth a thousand words. So take off the face mask, and look at the skin!

Keywords: face mask, COVID-19, pandemic, skin damage

INTRODUCTION

Prolonged and tightly use of face masks has been identified as cause for skin damage during the COVID-19 pandemic, many papers describing allergic and contact dermatitis, urticaria, xerosis, and exacerbation of preexisting skin diseases.[1] Furthermore, it has been stated that there is also a pandemic of dermatitis caused by personal protective equipment, especially face masks.[2]

CASE SERIES PRESENTATION

We evaluated patients seen in outpatient conditions between March and May 2020, during the lockdown period for the SARS-CoV-2 pandemic, focusing on skin damage related to the use of face masks. Our aim was to highlight the major impact of routine usage of face masks on the skin of individuals of different

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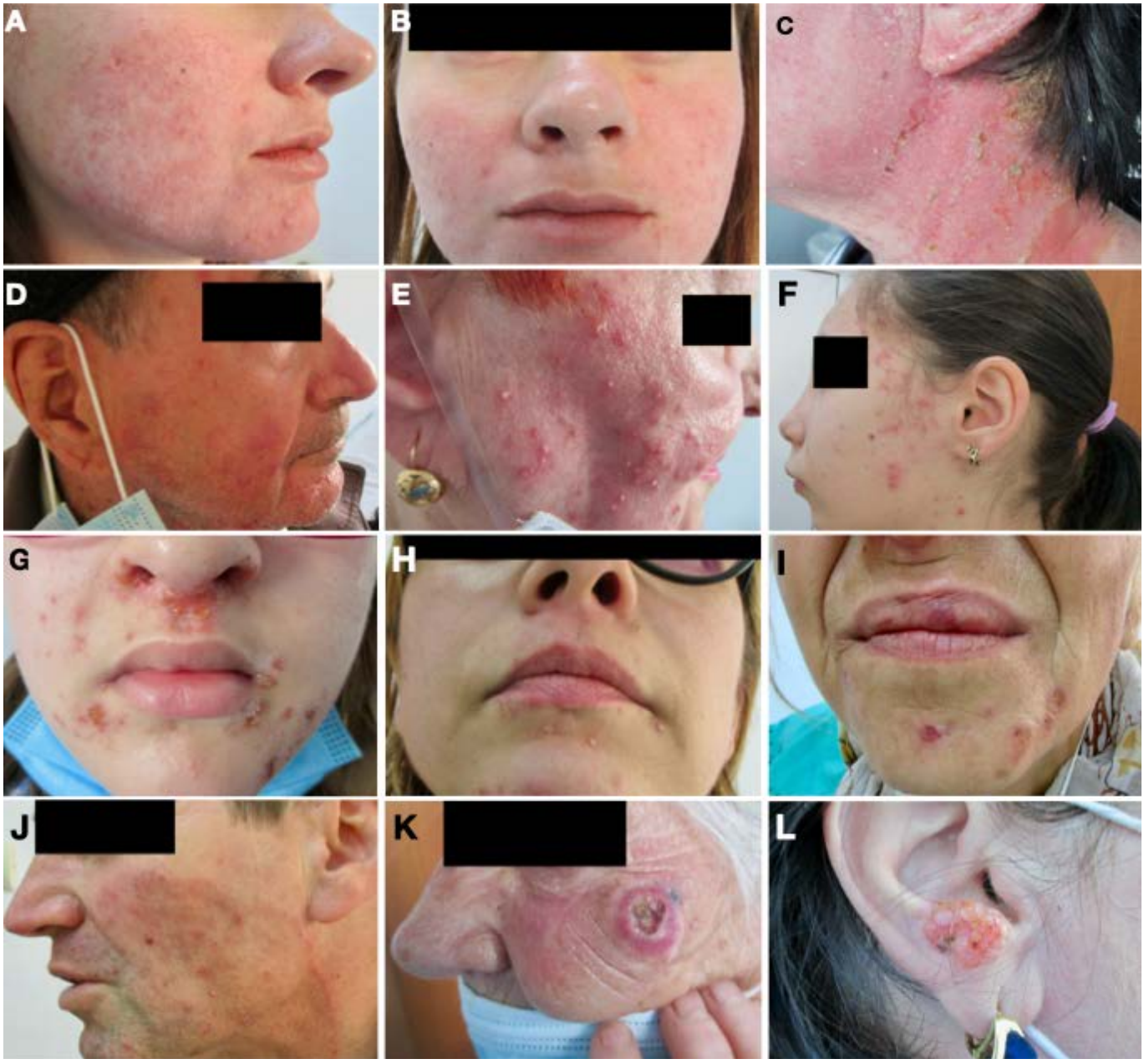

FIGURE 1. **Case 1:** Irritant contact dermatitis in a young nurse, with no history of skin disorders and no allergic background; patch test proved to be negative to standard battery and to textile series, formaldehyde, and thiuram, she has been working in an intensive care unit using FFP1-type masks; systemic antihistamines and emollients showed slight improvement (**A**, **B**). **Case 2:** Allergic contact dermatitis in a middle-aged woman, non-healthcare worker, who was seen in the emergency department for a bacterial impetiginized eczema of the left side of the face and neck; she was initially treated with systemic antibiotics (amoxicillin 2 g/day for 7 days) and potent topical steroids; she admitted prolonged use of a cloth homemade mask and denied any other morbidities or drug intake; she was sent to the allergy department and tested; the results showed positivity to formaldehyde; she was advised to change the type of face mask to single-use surgical mask (**C**). **Cases 3–6:** Flare-up of preexisting skin diseases: seborrheic dermatitis in a 67-year-old male patient (**D**), pustular rosacea in a 56-year-old nurse (**E**), acne in a teenager (**F**), perioral dermatitis in a 23-year-old student (**G**) and a 34-year-old physician (**H**), all very anxious about the burst of "silent" skin disorders. **Case 7:** Neurotic excoriations were frequently diagnosed, especially in women, with self-inflicted lesions on the face when the mask was taken off and anxiety was at high levels; psychiatric examination was required to each case (**I**). **Case 8:** Humidity and friction were in favor of developing a fungus infection on the face, in a field laborer working in the midday wearing a paper face mask; direct mycological examination was positive (**J**); **Cases 9–10:** Due to lockdown and privation of medical access many severe cases of basal cell carcinoma (BCCs) were covered by face masks in a 67-year-old woman and a 43-year-old woman; the lesions were certainly present prior to the pandemic but were not so aggressive locally (**K, L**).

ages and professions. We found that contact dermatitis was prevalent, but we also recorded many cases of outbreak of seborrheic dermatitis, acne, rosacea, perioral dermatitis, atopic dermatitis, and folliculitis. Neurotic excoriations caused by anxiety (self-reported and certified by psychiatric evaluation) and delayed diagnosis of benign and malignant tumors, especially basal cell carcinoma, due to the lockdown, were present in high numbers.

Prolonged contact of facemasks and humidity, during summer days, were in favor of developing severe cases of tinea, especially in diabetic patients. Impetigo and simple pruritus sine material were also present, many patients complaining of diffuse itching without skin marks (Figure 1).

The current brief report was approved by the Ethics Committee of the Institution where it was conducted, and all study procedures and questioning were performed according to the Declaration of Helsinki. Informed consent for patient information and images to be published was obtained.

CONCLUSIONS

The most important step should be the assessment of dermatologic pathology related to the use of face masks. They say a picture is worth a thousand words. So take off the face mask, and look at the skin!

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Yan Y, Chen H, Chen L, et al. Consensus of Chinese experts on protection of skin and mucous membrane barrier for health-care workers fighting against coronavirus disease 2019. *Dermatol Ther*. 2020;e13310.
2. Balato A, Ayala F, Bruze M, et al. European task force on contact dermatitis statement on coronavirus disease-19 (COVID-19) outbreak and the risk of adverse cutaneous reactions. *J Eur Acad Dermatol Venereol*. 2020;34:e353-e354.

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