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The Prevalence of extraintestinal manifestations in Inflammatory Bowel Disease

1. Aleksandra Madej MD, ORCID: 0009-0006-7757-8363, University Hospital, Zyty 26, 65-046 Zielona Gora, Poland, aleksandmad@gmail.com

2. Hanna Senat MD, ORCID: 0009-0009-3862-5827, Miedziowe Centrum Zdrowia S.A. Marii Skłodowskiej - Curie 66, 59-300 Lubin, hannasenat1@gmail.com

3. Patrycja Grabowska MD, ORCID: 0009-0000-3171-2746, Voivodeship Specialist Hospital of the NMP, Bialska 104/118, 42-202 Czestochowa, Poland grabowska0903@gmail.com

4. Patrycja Bolla MD, ORCID: 0009-0009-6118-2104, Faculty of Medicine, Wroclaw Medical University, Wybrzeze L. Pasteura 1, 50-367, Wroclaw, Poland, patrycjabolla@gmail.com

5. Aleksandra Senat, ORCID: 0009-0000-2523-4370, Faculty of Medicine, Wroclaw Medical University, Wybrzeze L. Pasteura 1, 50-367, Wroclaw, Poland, ola.senat@gmail.com

6. Zuzanna Marczyńska MD, ORCID: 0009-0007-5162-9836, Faculty of Medicine, Wroclaw Medical University, Wybrzeze L. Pasteura 1, 50-367, Wroclaw, Poland, zuzia.marczynska@gmail.com

Corresponding author
Aleksandra Madej MD,
+48-790212058, aleksandmad@gmail.com
University Hospital, Zyty 26, 65-046 Zielona Gora

ABSTRACT:

INTRODUCTION: The term inflammatory bowel disease (IBD) refers to a chronic inflammatory disease of the gastrointestinal tract of unclear pathogenesis. IBD consists of ulcerative colitis (UC) and Crohn's disease (CD). The two most common manifestations of the disorder, both have a chronic course with episodes of acute activity. Their underlying pathogenesis and symptoms, however, are quite distinct. IBD has a multiple factor etiology involving genetics, immunological dysregulation and dysbiosis of the intestinal microbiome. The resulting chronic inflammation of the entire body is the cause of the symptoms and signs of the condition. Extraintestinal manifestations (EIM) occur in 5% to 50% of IBD patients over the course of their lifetime.

PURPOSE: The aim of the study is to present the current state of knowledge about the prevalence of extraintestinal manifestations in Inflammatory Bowel Disease.

MATERIALS AND METHOD: The available literature in PubMed was reviewed to write the article, using the keywords „inflammatory bowel disease", „Crohn's disease", „ ulcerative colitis", „extraintestinal manifestations IBD".

CONCLUSION: Extraintestinal manifestations are evidence that IBD is not only confined to the intestine, these may involve many different organs other than the gut and may be more devastating than the IBD. Screening for EIM in these patients and prompt adequate treatment are essential. To adequately manage EIM and improve the quality of life of our patients, appropriate treatment regimens and therapies are required in a multidisciplinary team approach. Due to the lack of available dedicated diagnostic biomarkers for EIM, consideration of concomitant extraintestinal conditions in patients with inflammatory bowel disease might help in the selection and management of them. Clinicians caring for patients with IBD must be aware of these various systemic manifestations, as failure to diagnose and treat them early can result in significant morbidity.

Keywords: IBD, Crohn's disease, ulcerative colitis, drugs used in IBD, PSC

1. Introduction

The term inflammatory bowel disease (IBD) refers to a chronic inflammatory disease of the gastrointestinal tract of unclear pathogenesis. IBD consists of ulcerative colitis (UC) and Crohn's disease (CD). The two most common manifestations of the disorder, both have a chronic course with episodes of acute activity. Their underlying pathogenesis and symptoms, however, are quite distinct. IBD has a multiple factor etiology involving genetics, immunological dysregulation and dysbiosis of the intestinal microbiome. The resulting chronic inflammation of the entire body is the cause of the symptoms and signs of the condition. EIM occur in 5% to 50% of IBD patients over the course of their lifetime. EIM occur in 31 percent of patients with Crohn's disease and 43 percent of patients with ulcerative colitis and are more common in women than men. The overall incidence of EIMs is decreased in the pediatric population compared to the adult population. One EIM is seen in 63% of patients during their lifetime, while two EIM are reported in 27% of IBD patients. (1-4)

Arthritis is the most frequent of all EIM, closely followed by aphthous mouth ulcers and uveitis. There is a genetic component to EIM, as those with siblings and 1st-degree family members with IBD are more prone to develop these conditions. IBD and its EIMs have been linked to the existence of certain major major histocompatibility loci. HLA-A2, HLA-DR1 and HLA-DQw5 are related to EIM in Crohn's disease, while HLA-DR103 is related to EIM in ulcerative colitis. Different HLA groups have been found to be involved in specific EIM, such as PSC and AS with HLA-B8/DR3 and HLA-B27, for example. Modification of the native microbiota has been implicated in the development of intestinal inflammatory disease in animal models of IBD, although its relevance in humans remains unknown.(5-12)

2. The purpose of the study

The aim of the study is to present the current state of knowledge about the extraintestinal manifestations of Inflammatory Bowel Disease.

3.Materials and method

The available articles were reviewed for their clinical relevance to the role of gut microbiota in patients with type 2 diabetes mellitus. The eligible English-language publications retrieved from the PubMed database were reviewed by using key words in different

combinations: „inflammatory bowel disease", „Crohn's disease", „ulcerative colitis", „extraintestinal manifestations IBD".

4. State of knowledge

4.1. Ocular manifestations

Episcleritis refers to the inflammation of the eye's cornea and is the most common ocular presentation of IBD. This condition is closely associated with the disease activity and acute flares. IBD may be considered in patients with IBD presenting with sudden flushing of one or both eyes accompanied by slight ocular discomfort, irritation, or burning. Ophthalmological findings include erythematous sclera with white scleral spots interspersed with dilated episcleral blood vessels.(12,13)

Uveitis is the name for acute inflammation of the uveal or middle layers of the eye, including the iris, ciliary body, and choroid. Depending on the anatomic site of involvement, uveitis is classified as anterior, intermediate or posterior. The anterior is when the anterior segment is involved, the middle is when it involves the vitreous, and the posterior is when it concerns the retina and choroid.(12,14-15)

A serious eye disease, scleritis is an infection of the deeper blood vessels of the sclera. Occurring in less than 1% of patients, scleritis can result in loss of vision, making it critical that it be recognized and treated promptly. The symptoms are eye redness, sensitivity to touch, and severe pain.(15)

It appears clinically as reddish or purplish spots on a background of continuous scleral redness. Furthermore, the scleral vessels fail to blanch with the administration of topical adrenaline. This situation is relatively serious and may result in retinal detachment and inflammation of the optic nerve. This condition should be treated with intensive systemic steroids, nonsteroidal anti-inflammatory drugs and immunomodulatory drugs to prevent vision loss, and the individual should always be seen by an ophthalmologic specialist.(12-15)

The eye problems that accompany acute flares of IBD are responsive to treatment of the gastrointestinal disease. In certain cases, however, therapies such as steroids, immunosuppressive therapy, and anticholinergics can cause ocular side effects. System administration of steroids is accompanied by a variety of side effects, and in the ocular system

they may cause posterior subcapsular cataracts, especially with prolonged administration. Usually, symptoms are minor or absent. Moreover, they are associated with elevated intraocular pressure, which increases the risk of developing open-angle glaucoma. Although more commonly this is seen when topical steroids are used. Immunosuppression may result in optic neuritis, ophthalmoplegia and nystagmus, particularly in the use of cyclosporine and methotrexate. (13-16)

4.2. Musculoskeletal manifestations

Arthralgia is more frequent than arthritis in IBD. Fibromyalgia manifests as widespread pain throughout the body, not confined to the joints. The physical examination reveals diffuse soft tenderness; the diagnostic features are currently determined by a generalized pain score and a severity of symptoms score. Diagnosis may be based on physical examination. No imaging is required in the majority of cases. Local radiographs may demonstrate erosive lesions with spurs and ossifications of entheses in the advanced phase. Increasingly, musculoskeletal ultrasound (MSU) is being used in the diagnosis and follow-up of enthesitis. MSU findings consistent with enthesitis are tendon edema, tendinitis, tendon calcifications, raised Doppler power signal, bony enthesal erosions, and adjoining bone marrow edema. Improving the MSU procedure by the addition of B-mode power Doppler or contrast-enhanced ultrasonography enhances the diagnostic precision of MSU for the evaluation of enthesitis, thereby becoming a highly specific diagnostic method.(17-18)

There are two different forms of peripheral arthritis that have been reported in relation to IBD. Peripheral arthritis type 1, an asymmetrical oligoarthritic, is more frequent and is typically related to attacks of IBD. Type 2 peripheral arthritis, on the other hand, presents as a symmetric progressive polyarthritis and is unrelated to intestinal inflammation. It is more invasive and can result in erosions. Symptoms of peripheral arthritis include joint pain and swelling of one or more joints, which may or may not be accompanied by morning stiffness. Physical examination of the involved joints can reveal evidence of inflammation - warmth, erythema, tenderness to palpation, and synovitis with or without effusion.(19)

Treatment aims of peripheral arthritis are to decrease pain, swelling, and stiffness and to maintain function. Peripheral arthritis type 1 is usually self-limiting and resolves with management of the primary IBD flare. Treatment of type 2 PAD typically involves a more intensive course of therapy.(20-21)

A common appendicular presentation of spondyloarthropathy in IBD patients, enthesitis is inflammation at the tendon insertion into the bone. It presents clinically as pain and swelling at the insertion of the Achilles tendon into the calcaneus, the insertion of the plantar fascia into the heel, or the insertion of the patellar tendon into the knee. (20-21)

4.3. Hepatobiliary manifestations

Approximately 50% of patients with IBD develop hepatobiliary manifestations during the course of the disease. These manifestations may be primary sclerosing cholangitis (PSC), autoimmune/granulomatous hepatitis, fatty liver disease, cholestasis, gallstone formation and autoimmune pancreatitis. PSC represents the most frequent hepatobiliary form of IBD, as 75% of patients with PSC are reported to have IBD. PSC leads to intrahepatic and extrahepatic biliary inflammation and fibrosis. Patients present with abdominal pain, fever, fatigue and decreased weight. The liver tests demonstrate a biliary steatosis pattern, with MRI showing the multiple segmental bile duct narrowing and dilatation. In advanced disease, liver cirrhosis, portal hypertension and liver failure are inevitable. PSC advances independently of intestinal IBD activity, and therefore IBD therapy does not help the situation. PSC is treated with ursodeoxycholic acid, endoscopic retrograde cholangiopancreatography with biliary dilatation, or liver transplant. Nearly half of patients with PSC may be symptomless at diagnosis and the disease is detected following routine liver tests. This is common in inflammatory bowel disease patients who have laboratory testing performed as part of their regular treatment. Examination may reveal jaundice, liver enlargement, splenomegaly, and scratch lesions. Lab tests typically show a cholestatic pattern with elevated serum alkaline phosphatase (AP) and gamma-glutamyl transpeptidase, while aminotransferases may also be increased. Of importance, a normally elevated level of AP does not exclude PSC. Several auto-antibodies have been implicated in PSC, however, their application and evaluation in the clinical setting is uncertain and they are unlikely to be involved in the pathogenesis of the disease. Angulo et al (22) found that antinuclear antibodies, anti-neutrophil cytoplasmic antibodies (especially those with perinuclear staining), anti-cardiolipin antibodies (hypergammaglobulinemia), rheumatoid factor, and thyroid peroxidase antibodies were present in a much greater percentage of patients with PSC in comparison with control subjects. The autoantibodies were found independent of the occurrence of IBD and, with the possible except of anticardiolipin antibodies, were not associated with the intensity of the disease. (20-22)

2.4. Dermatological manifestations

Related cutaneous conditions are those that are quite common in IBD patients. The pathophysiological underlying processes are linked to the chronic inflammatory condition and the presence of specific human leukocyte antigen (HLA) genes, for instance HLA-DR2 and HLA-B27.(23)

Certain mucocutaneous presentations are an extension of the inflammation of the intestinal tract and share the histologic features, such as non-caseating granulomas, dermal infiltrates containing large numbers of multinucleate cells, lymphocytes, and eosinophils. These are present exclusively in CD, as UC never extends to the external mucosal layers. (23,24)

Erythema nodosum is the most frequent skin presentation, occurring in up to 3%-10% of patients with ulcerative colitis (UC) and 4%-15% of patients with Crohn's disease (CD), most commonly in women between the ages of 25 and 40. It is believed to be a late cellular hypersensitivity reaction induced by various antigenic stimulations that begins with an abrupt eruption of erythematous, warm, painful, non-ulcerative nodules that sometimes fuse to form erythematous plaques. The lesions are usually symmetrical and bilateral, and the color tends to change - first bright red, then purpuric, then yellow. It can be associated with systemic manifestations such as fever, myalgias, arthralgias, headache, gastrointestinal symptoms, fatigue, or cough, and other less common manifestations include hepatomegaly, splenomegaly, and pleuritis. Nodules are most commonly found on the extensor surfaces of the lower extremities. Although any part of the body-facial, trunk, and upper extremities can be affected. They are usually diagnosed by clinical appearance without biopsy. The lesions typically last three to six weeks and disappear without leaving a scar. During its course, elevation of the legs and bed rest are advised, and nonsteroidal anti-inflammatory drugs are first-line treatment for pain.(23-28)

Abscesses, fistulas, fissures and ulcers are the most common manifestations and contribute significantly to the incidence of CD. In 36% of patients, perianal lesions are observed. They can manifest as erythema, fissure, perianal stenosis, fecal incontinence, abscess, and fistula (the latter two being more common). These changes can also be seen in the peristomal region and in the abdominal scars caused by laparotomy or umbilical scars forming enterocutaneous fistulae. Oral lesions are observed in 8-9% of patients; these are mainly angular cheilitis,

straight and deeply cut lip ulcers, lip and tongue fissures, gingival nodules, cobblestone-like oral mucosa and painful inflammation of the gingiva.(23-28)

Pyoderma gangrenosum is seen in about 1%-2% of patients and is more commonly found in association with ulcerative colitis. It occurs more frequently in women. The pathogenesis is not fully understood, but it is thought to be an autoinflammatory process related to an abnormality in innate and adaptive immune function. Together with Sweet's syndrome, it is characterized as a neutrophilic dermatosis resulting from the accumulation and activation of neutrophils in the skin and is less commonly seen in the inner organs. It initially appears as papules, pustules, or nodules that rapidly ulcerate to form a painful lesion with violaceous margins that spreads in a peripheral direction. Though it can affect any part of the body, the lesions are more common on the legs and in the peristomal region and are generally associated with trauma, known as the patergia phenomenon. The diagnosis of this disease is difficult because of the large number of possible differential diagnosis; thus, a careful physical examination and biopsy are necessary. Biopsy usually reveals a neutrophilic infiltrate with peripheral lymphocyte deposition. Management begins with local steroid therapy, wound care, and a calcineurin inhibitor; early initiation of systemic steroids and cyclosporine may be necessary. Sweet's syndrome is more common in females, in the third to fifth decade of life, and is more common in CD. Although primarily described as an erythematous papule or plaque, vesicles and pustules may be seen on the skin of the face, neck, and upper extremities during the natural history of the disease; less commonly, they have been reported in the esophagus, duodenum, and colon. Most patients have cutaneous manifestations accompanied by systemic signs such as fever, arthralgias, myalgias, headache, conjunctivitis, and oral ulcers. Bowel-Associated Dermatosis-Arthritis Syndrome (BADAS) is a neutrophilic dermatosis whose etiology remains unknown. It is believed to be caused by excessive intestinal bacterial overgrowth, which leads to immune complex deposition in the skin and joint membranes, causing inflammation. The clinical presentation is defined by repeated attacks of asymmetrical, nondestructive arthritis, typically of a multiarticular character in the upper extremities, that may be combined with tendinitis. Cutaneous involvement is usually on the upper trunk and upper limbs and is marked by erythematous, painful papules and plaques, sometimes pustules and aseptic vesicles. The lesions are often presented with fever, malaise, abdominal pain, diarrhea, and malabsorption. On histology, they appear as peripheral vascular neutrophilic infiltrates with histiocytes containing polymorphonuclear fragments called nuclear dust in their cytoplasm and dermal edema. Management consists of antibiotics,

systemic steroids, dapsone and sulphapyridine, and restoration of the intestinal structure by operation.(23-28)

Oral stomatitis occurs in about 10% of IBD patients, most commonly in CD, but more frequently in UC. Ulcers may occur as a result of CD expansion with classic granulomatous inflammation or as a result of nutrient deficiencies secondary to malabsorption in the course of IBD. In fact, a study recently reported that B12, folic acid, and iron deficiencies, either concurrently or alone, are related to AFS in patients of all age groups. Aphthous stomatitis is a common oral disease that is described as multiple, painful, round/oval ulcers with a yellow pseudomembranous base and erythematous margins. These ulcerations are commonly found in the oral or labial mucosa; their characteristic appearance renders histopathologic evaluation in patients with IBD unnecessary. Between seven and eleven percent of IBD patients suffer from psoriasis, an erythematous/scaly condition that is more common in CD than in UC. IBD is more likely to occur in patients with psoriasis, and there's a higher risk of iatrogenic psoriasis involvement in patients with IBD treated with anti-TNF therapy. The most frequent subtype is plaque psoriasis (plaque psoriasis or chronic plaque psoriasis). The lesions are typically monomorphous, with well-demarcated erythematous plaques topped by silvery scales that can be sparse or appear as erythroderma involving the entire body surface. It may involve any area of the skin, but is typically located on the flexor surface of the forearms and legs, periumbilical, perianal, retroauricular, and scalp areas. Anti-TNF agents have been used with success in the treatment of both psoriasis and IBD, as TNF plays an integral part in the development of both diseases - infliximab, adalimumab and certolizumab can all cause disease remission in both conditions.(24-27)

5. Conclusion:

Extraintestinal manifestations are evidence that IBD is not only confined to the intestine, these may involve many different organs other than the gut and may be more devastating than the IBD. Thorough screening for EIM in these patients and prompt adequate treatment are essential to prevent disability. To adequately manage EIMs and improve the quality of life of our patients, appropriate treatment regimens and therapies are required in a multidisciplinary team approach. Due to the lack of available dedicated diagnostic biomarkers for EIMs, consideration of concomitant extraintestinal conditions in patients with inflammatory bowel disease might help in the selection and management of them. Clinicians caring for patients with IBD must be aware of these various systemic manifestations, as failure to diagnose and treat them early can result in significant morbidity.(29-33)

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Author contributions

Conceptualization, A.M., H.S. ; Methodology, P.G. and A.M. ; Validation, P.B. and A.S. ; Formal Analysis, Z.M,; Investigation A.M; Resources, A.M. ; Data Curation, H.S. and A.M. ; Writing – Original, A.M. ; Writing – Review & Editing, A.M. and A.S. ; Visualization, P.B. and P.G. ; Supervision, A.S.; Project Administration H.S.,

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The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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Informed consent was obtained from all subjects involved in the study.

Data availability

The data have not been made public, but are kept with the authors, if necessary.

Ethics approval

Written informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

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