Extra-intestinal manifestations in inflammatory bowel disease: Etiopathogenesis and management

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Abstract

Inflammatory bowel disease (IBD) can be considered a systemic inflammatory disease since it can present with a variety of extra-intestinal manifestations (EIMs). Arthropathies are the most common manifestation, but EIMs can occur in a wide variety of organs. The relevance of EIMs lies in its impact on quality of life. Even some EIMs may be associated with a decreased survival as occurs in primary sclerosing cholangitis (PSC), which is related to an increased risk of cholangiocarcinoma. The pathogen of EIMs is still partially unknown and treatments are not always effective. Some EIMs follow the course of the intestinal activity and may be treated as an intestinal flare. Others have an independent course and are difficult to treat. In this article, we review the pathogenesis of EIMs, their clinical manifestations, and the available treatments.

Keywords: Inflammatory bowel disease. Extra-intestinal manifestation. Crohn's disease. Ulcerative colitis.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are systemic inflammatory diseases that mainly affect the gastrointestinal tract but can manifest with extra-intestinal symptoms in up to 50% of patients¹. These extraintestinal manifestations (EIMs) have a significant impact on the quality of life of patients and, in the case of primary sclerosing cholangitis (PSC), on survival due to an increased risk of neoplasia². EIM can be diagnosed before, after, or simultaneously with inflammatory bowel disease (IBD). There are even some very specific EIMs (like PSC) that should make us actively search for an underlying IBD¹. EIMs affect multiple organs (such as skin, eyes, muscles, joints, liver, and bile duct) and can run a parallel or independent course from intestinal activity^{3,4}.

In this article, we review the epidemiology and pathogen of EIMs and describe the most frequent EIMs as well as their current management.

Epidemiology

Between 6 and 47% of patients with IBD develop at least one EIM throughout their lives, with arthralgia/arthritis being the most frequent EIM⁵⁻¹³. The prevalence of the most frequent EIMs is described in [table 1](#). It is more common in patients with CD than with UC and affects more women¹³⁻¹⁵.

The likelihood of developing EIMs increases with the duration of bowel disease and is higher in patients who already have another EIM¹³. In most patients, EIMs occur after IBD diagnosis, but about 25% of cases appear before it¹.

Pathogenesis

The pathogenesis of EIMs is still partially unknown. There are two theories that explain the development of these manifestations. The first describes the occurrence of extraintestinal symptoms as the extension of a specific immune response to other systems. The

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Table 1. Prevalence of the most frequent EIMs^{40,41,51,53}

Axial arthropathy	Up to 25%
Peripheral arthropathy	5-20%
Erythema nodosum	Up to 15%
Pyoderma gangrenosum	0,4-2%
Episcleritis	2-5%
Anterior uveitis	0,5-3%
Primary sclerosing cholangitis	4-5%
Osteoporosis	4-9%

second argues that EIMs are independent inflammatory processes but that appear as a consequence of IBD or by shared environmental or genetic factors. Most likely, several pathogenic mechanisms are involved in the development of EIMs¹⁶.

Extension of specific immune response from the intestine

It has been demonstrated an ectopic expression of cytokines and adhesion molecules that in healthy patients are limited to the intestine. Specifically, the ectopic expression of MAdCAM-1 and CCL25 has been identified in the vascular endothelium of the portal tract of patients with PSC associated with IBD^{17,18}.

Another pathogenic mechanism in this sense is the increase in chemokines and adhesion molecules non-specific of the gastrointestinal tract that can lead to the recruitment of intestinal leukocytes at an extra-intestinal site^{16,19}.

There could be an immune reaction on other systems mediated by circulating antibodies and immune complexes. Shared epitopes of the colon with other organs (eyes, joints, skin, and biliary epithelium) have been found²⁰⁻²². However, this causal mechanism in the development of EIMs has not been demonstrated yet.

Finally, the translocation of microbial antigens derived from the intestinal microbiota could be another pathogenic mechanism. Patients with IBD-associated PSC have a different gut microbiota and the transport of microbial antigens into the portal circulation could activate an immune response through $\alpha 4\beta 7$ -MAdCAM-1^{23,24}.

Independent inflammatory events

Patients with IBD have increased mucosal and systemic levels of pro-inflammatory mediators such as interleukin (IL)-6, tumor necrosis factor (TNF- α),

interferon, and vascular endothelial growth factor, as well as bacterial lipopolysaccharide (LPS) that can promote immune activation in other systems²⁵. The innate immune system is also involved through a phenomenon called “neutrophil priming”²⁶, which means that neutrophils present a greater response when activated and produce a higher amount of IL-1 β and TNF- α . In addition, there could be an alteration in hematopoiesis²⁷.

The intestinal microbiota seems to be related to the development of EIMs. Some of the mechanisms that could be involved in this would be translocation of bacteria or microbial products such as LPS due to an alteration of the intestinal barrier, and the production of metabolites derived from the microbiota that stimulate the immune system²⁸⁻³⁰.

Musculoskeletal manifestations

Arthropathies associated with IBD are the most frequent EIM and are included in the group of spondyloarthropathies. They are divided into axial and peripheral. They must be differentiated from arthralgias, which are a very common symptom in patients with IBD. In addition to these two forms that will be explained below, patients with IBD may have drug-induced joint symptoms. Treatment with corticosteroids increases the risk of osteoporosis and avascular bone necrosis, and anti-TNF treatment is associated with a lupus-like phenomenon².

Axial arthropathy

Axial arthropathy is usually independent of IBD. Axial involvement is characterized by sacroiliitis that can be accompanied by vertebral involvement and includes a spectrum of entities from non-radiological axial spondyloarthropathy to ankylosing spondylitis (Fig. 1). Its prevalence ranges between 12% and 46% of patients with IBD and an association with HLA-B27 has been demonstrated, especially in patients with ankylosing spondylitis³¹⁻³³.

Peripheral arthropathy

Peripheral arthropathy has been classically classified into pauciarticular or type 1 and polyarticular or type 2. Type 1 affects fewer than 5 joints and usually manifests in large joints, especially knees. The course of this type of arthropathy runs in parallel with intestinal activity and is usually self-limited, with a duration of < 10 weeks. Type 2 affects five or more small joints, the metacarpophalangeal joints being the most common. The course of type 2 arthropathy is independent of IBD activity, and symptoms tend to last longer than in type 1^{10,34}.

Figure 1. Magnetic resonance imaging of the sacroiliac joints of a 17-year-old patient with Crohn's disease and with back and left sacroiliac pain. **A:** sequences T1-weighted images and **B:** STIR shows bilateral sacroiliac osteitis.

Figure 2. Anti-TNF-induced psoriasiform dermatitis.

Treatment

The European consensus document of the European Crohn's and Colitis Organization (ECCO)² recommends for the treatment of axial arthropathy intensive physical therapy and short-term nonsteroidal anti-inflammatory drugs (NSAIDs). They do not recommend keeping NSAIDs in the long term² because the use of these drugs has been associated with an increased risk of intestinal disease flares^{4,35}. COX-2 inhibitors are presented as an attractive alternative to NSAIDs in patients with IBD^{36,37}. Other treatments such as mesalamine are not effective in the treatment of arthropathies associated with IBD and therefore anti-TNF should be used early².

Recommendations for the treatment of peripheral arthropathy include treatment of intestinal inflammation, short-term NSAIDs, and local infiltration with corticosteroids. Other alternatives in these patients are short-term oral corticosteroids, sulfasalazine, methotrexate, or anti-TNF².

Oral and cutaneous manifestations

These manifestations are diverse and are divided into several groups: manifestations with the same histology as IBD (metastatic CD), reactive manifestations (erythema nodosum, pyoderma gangrenosum, and Sweet's syndrome), dermatoses associated with IBD (psoriasis), and manifestations secondary to pharmacological treatment, especially secondary to anti-TNF (Table 2 and Fig. 2)³⁸. The most frequent orocutaneous manifestations are described below.

Erythema nodosum

The diagnosis is based on the typical clinical presentation as raised subcutaneous nodules, red or purple,

hot, painful and between 1 and 5 cm. Nodules are usually located in the pretibial region². The appearance of this lesion is mostly accompanied by intestinal disease activity, although the severity of the erythema nodosum does not correlate with the severity of the intestinal symptoms³⁹. When the presentation or location is not typical, a skin biopsy can be used. Metastatic CD, Behçet's disease, sarcoidosis, and skin infections should be considered in the differential diagnosis of EN⁴⁰.

Erythema nodosum usually resolves with an effective treatment for the bowel disease.

Pyoderma gangrenosum

It occurs more frequently in UC than in CD. Pyoderma gangrenosum presents as one or multiple erythematous and painful papules or pustules that progress to deep ulcers with sterile exudate. The most frequently affected areas are the pimples and the peristomal skin. The clinical course is not always parallel to that of intestinal activity. The diagnosis is made by the clinical presentation and by the exclusion of other diseases. Biopsy can help to exclude other cutaneous diseases even though findings are non-specific. Skin biopsy may not be needed if the clinical presentation is typical and if there is a good response to treatment⁴⁰. Treatment will include systemic corticosteroids and, in refractory cases, infliximab, adalimumab, or oral or topical calcineurin inhibitors².

Sweet syndrome

Also known as acute febrile neutrophilic dermatosis, it is a rare cutaneous EIM. It presents as soft, erythematous papules or nodules. Sweet syndrome usually runs in parallel with the intestinal activity⁴⁰. Treatment is based on systemic corticosteroids and in refractory cases, immunosuppressants².

Table 2. Anti-TNF-induced skin lesions

Paradoxical skin reactions:
– Eczematiform
– Psoriasiform
Infusion reactions and injection site reactions
Lupus-like syndrome
Cutaneous malignancies
Skin infections

Oral lesions

Oral involvement is common in patients with IBD, and some of the following lesions may occur aphthous stomatitis, periodontitis, and vegetative peristomatitis. Oral lesions parallel intestinal disease activity, so the treatment will be that of the latter⁴⁰.

Ophthalmological manifestations

After the joints and the skin, the eye is the organ most affected by EIMs. Within this kind of EIMs, episcleritis (Fig. 3) and anterior uveitis are the most frequent. Other ophthalmological manifestations such as scleritis (Fig. 4) or intermediate or posterior uveitis are much more infrequent. Episcleritis refers to the appearance of erythema in the sclera and conjunctiva and is usually painless. Anterior uveitis is less frequent and in patients with IBD, it is more frequently bilateral and of insidious onset. Associated symptoms are eye pain, blurred vision, photophobia, and headache. Normally, episcleritis parallels intestinal activity while uveitis runs an independent course³.

Treatment of episcleritis is the same as for IBD; topical or oral NSAIDs and topical corticosteroids are used to manage symptoms. On the other hand, uveitis deserves prompt referral to an ophthalmologist; topical corticosteroids may be used initially to reduce inflammation and topical cycloplegics to avoid spasms of the ciliary body and pupil and prevent the formation of synechiae. In refractory cases, systemic corticosteroids, immunosuppressants, or biologicals agents may be required^{2,41}.

Hepatobiliary manifestations

The most common liver EIM is PSC. Even so, it should be noted that a percentage of patients with IBD may have an altered liver profile and first, hepatotoxicity (DILI) and other causes of liver disease independent of IBD must be ruled out.

Figure 3. Episcleritis. **Figure 4.** A: active scleritis. B: inactive scleritis with sclera thinning.

Primary sclerosing cholangitis

The diagnosis of PSC is made in a patient with cholestasis (elevated alkaline phosphatase is the most frequent laboratory finding) and typical features in magnetic resonance cholangiography (MRC), including multifocal intra- and extra-hepatic biliary strictures, once the causes of secondary sclerosing cholangitis have been ruled out (Table 3). In patients with normal MRC, a liver biopsy should be used to diagnose the small-duct PSC variant, which is characterized by normal appearance of the biliary tract in MRC^{2,42}.

Between 24 and 96% of patients with PSC are positive for atypical perinuclear antineutrophil cytoplasmic auto-antibody (p-ANCA)⁴². However, this marker is not specific to this disease nor do they have prognostic significance. In those patients with elevated antinuclear antibodies, anti-smooth muscle antibodies, or increased immunoglobulin G, we should suspect the existence of autoimmune hepatitis (AIH) and perform a liver biopsy. If IgG4 concentrations are high (more than 4 times the normal value) or the IgG4/IgG1 ratio is increased, we should suspect sclerosing cholangitis associated with IgG4^{2,43}.

As previously described, MRC is the diagnostic test of choice. The typical image shows short multifocal strictures in the intra- and extra-hepatic bile ducts. Endoscopic retrograde cholangiopancreatography (ERCP) is reserved for the treatment of strictures and to rule out cholangiocarcinoma (taking biopsies and brushing). In the case of ERCP, it is recommended to use prophylactic antibiotic therapy in all cases⁴³.

The diagnosis of PSC in a patient with IBD significantly worsens the prognosis. Complications associated with PSC are cholestasis, cholangitis, cholelithiasis, cholangiocarcinoma, colorectal cancer, osteoporosis, vitamin deficiency, and steatorrhea².

Regarding treatment, there are no drugs that have proven to prolong transplant-free survival in these patients. Even so, ursodeoxycholic acid is routinely used at intermediate doses of 15–20 mg/kg/day. This drug has been shown to improve cholestasis but not survival. High doses should be avoided. Corticosteroids and immunosuppressants can be used in patients with evidence of autoimmune hepatitis. The indications for liver transplantation in patients with PSC are decompensated liver disease, intractable pruritus, and recurrent bacterial cholangitis. Transplantation could also be considered in patients diagnosed of biliary dysplasia^{2,43}.

The follow-up of patients with PSC will be done with annual (or biennial) colonoscopy for colorectal cancer screening⁴³. There are no established recommendations for the early diagnosis of biliary neoplasms. In general, annual abdominal ultrasound is recommended to assess gallbladder lesions and perform additional tests (MRC, ERCP, and CT) if cholangiocarcinoma is suspected².

Cardiovascular manifestations

The incidence of cardiovascular events in patients with IBD is low but higher than in general population. This risk must be taken into account given the morbidity and mortality associated with these events. Even so, an increase in cardiovascular mortality has not been demonstrated in patients with IBD compared to the general population⁴⁴.

The cardiovascular manifestations are pericarditis, myocarditis, venous and arterial thromboembolism, arrhythmias, atrioventricular block, heart failure, endocarditis, valvular heart disease, and Takayasu arteritis. Pericarditis is the most common disease, representing 70% of cardiovascular manifestations⁴⁴. IBD patients have 1.2 times higher risk of myocardial infarctions than general population, 1.2 times the risk of stroke, and 3.5 times the risk of mesenteric ischemia^{45,46}.

Table 3. Causes of secondary sclerosing cholangitis

AIDS-related cholangiopathy
Cholangiocarcinoma
Choledocholithiasis
Chronic biliary infestation (liver fluke, ascaris)
Congenital causes (choledochal cysts, Caroli's syndrome, and biliary atresia)
Histiocytosis X
Cystic fibrosis
Eosinophilic cholangitis
IgG4-associated cholangitis
Ischemic cholangitis
Mast cell cholangiopathy
Portal hypertensive biliopathy
Recurrent pyogenic cholangitis
Sarcoidosis
Sclerosing cholangitis in critically ill patients
Surgical trauma

AIDS: acquired immune deficiency syndrome.

Venous thromboembolism (VTE) is approximately 3 times more common in patients with IBD than in the general population⁴⁷. It mainly affects the lower limbs and the pulmonary circulation. Risk factors are an increased Charlson Comorbidity Index, advanced age, immobility, smoking, anemia, corticosteroids, central venous catheters, oral contraceptives, hospitalization, and recent surgery. There is an increased risk of developing VTE during periods of IBD flare compared to periods of remission³. Treatment is the same as in the general population. To prevent VTE events, the European consensus document of ECCO² recommends antithrombotic prophylaxis for all patients with IBD admitted to a hospital and recommends to consider maintaining prophylaxis at discharge, after recent surgery and in outpatients with inflammatory activity^{2,44}.

A key aspect of preventing cardiovascular events in patients with IBD is the prevention of flares and maintenance of remission because systemic inflammation is associated with the development of arteriosclerosis and coronary heart disease⁴⁴.

Pulmonary manifestations

In those patients with IBD who present pulmonary symptoms in the first place, infections and

drug-induced lung injury, especially due to 5-aminosalicylic acid (5-ASA) and methotrexate, must be ruled out. Salicylates are associated with different types of interstitial lung disease. Methotrexate can cause hypersensitivity pneumonitis or pulmonary fibrosis. Lung damage has also been described with the use of azathioprine, 6-mercaptopurine, and anti-TNF. Treatment essentially lies in the suspension of the drug involved^{2,48}.

The pulmonary EIMs are rare. However, abnormalities found incidentally in respiratory function tests or chest imaging tests are relatively frequent. The EIMs of IBD usually affect the airway and can cause symptoms in any section of the respiratory tract from the glottis to small airways, most commonly affecting large airways. Lung interstitial damage can also occur, with organized pneumonia being the most common form. These manifestations usually respond adequately to treatment with inhaled or systemic corticosteroids. In refractory cases, immunosuppressants or biologicals may be used^{2,48}.

Renal and urological manifestations

Renal failure in patients with IBD may be due to drug toxicity or be an EIM of the disease, but this is difficult to differentiate. An association of IBD with the development of secondary amyloidosis, tubulointerstitial nephritis, and glomerulonephritis, especially IgA nephropathy, has been described. The risk of tubulointerstitial nephritis must be taken into account in patients treated with 5-ASA. Cyclosporine can cause acute and chronic kidney failure^{2,3,49}.

Patients with IBD, especially those with CD, have more commonly uric acid or calcium oxalate nephrolithiasis². An important proportion of IBD patients with nephrolithiasis has undergone surgery. Low urine pH and low urine volumes are risk factors associated with the development of uric acid stones. Patients with IBD have also a higher risk of calcium oxalate nephrolithiasis as a result of an increased intestinal oxalate absorption⁵⁰.

Osteopenia and osteoporosis

Osteopenia and osteoporosis are common in patients with IBD. The prevalence of osteoporosis varies between 4% and 9%. The diagnosis of osteoporosis is made when T-score is lower than -2.5 on a radiographic bone densitometry, whereas osteopenia is defined as a T-score between -1 and -2.5^{2,51}.

CD, a low body mass index, and low weight are risk factors associated with low bone mineral density (BMD) or osteoporosis⁵¹. Some measures such as wear bearing exercise, smoking cessation, and an adequate intake of

calcium in the diet (1 g/day) prevent the loss of BMD. The European consensus document of ECCO² recommends systematically calcium and Vitamin D in patients receiving systemic corticosteroids. Control of intestinal inflammatory activity is necessary to reduce bone loss. Bisphosphonate treatment has been shown to reduce the risk of vertebral fractures in patients with IBD. Even so, this treatment cannot be widely recommended in young patients and premenopausal women^{2,52}.

Conclusion

IBD is a systemic inflammatory disease that affects multiple systems other than the intestine. The symptoms, treatment, and prognosis of different EIMs are varied. Its pathogenesis is still unclear and its deeper knowledge would help us to better treat them. Some EIMs run an independent course from the IBD and can affect severely patient's quality of life, so the treating IBD physician should be aware to detect and control this EIM in due course.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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