Extraintestinal manifestations of inflammatory bowel disease: Clinical aspects and pathogenesis.

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Abstract

Background: Extraintestinal manifestations (EIM) are common in patients with inflammatory bowel disease (IBD). These manifestations can affect many organs, and joints, skin, eyes and hepatobiliary tract the most commonly affected sites. Among patients with IBD about 36% of them will have at least one EIM lifelong. Perianal Crohn's disease, colonic involvement and smoking are associated with susceptibility to the development of EIM.

Objective: This article reviewed the clinical aspects and the pathogenesis of main extraintestinal manifestations in IBD.

Methods: Bibliographical searches were performed in PubMed (January 1990–October 2017), using specific terms.

Conclusion: It is believed that the diseased gastrointestinal mucosa can trigger immune responses in extraintestinal sites due to shared epitopes in genetically susceptible individuals, although its pathogenesis is not fully understood.

Introduction

Inflammatory Bowel Disease (IBD), mainly represented by ulcerative colitis (UC) and Crohn's disease (CD) is a group of chronic diseases of unknown origin and spontaneously recurring. Immune-mediated mechanisms are involved in the pathogenesis of these disorders in genetically susceptible individuals. Among these mechanisms are include dysregulation of innate and adaptive immune responses directed against luminal bacteria or their products found in the intestinal lumen and changes in the intrinsic barrier function of the intestinal mucosa. However, despite recent advances in understanding the molecular mechanisms involved in the pathogenesis, the exact cause (s) of IBD remains elusive [1-4].

Extraintestinal manifestations (EIM) associated with inflammatory bowel disease are conditions often observed in patients with ulcerative colitis or Crohn's disease. These events may affect various organs and may develop before the onset of gastrointestinal symptoms [5-8]. The EIM affect most often the joints (peripheral and axial arthropathy), skin (erythema nodosum, pyoderma gangrenous, aphthous stomatitis), eyes (episcleritis, uveitis) and hepatobiliary tract (primary sclerosing cholangitis (PSC)) (Table 1). Other organs and systems, such as lungs, kidneys, pancreas and venous system are less frequently affected by EIM. Some extraintestinal manifestations such as arthritis pauciarticulares, the erythema nodosum, episcleritis and oral aphthous ulcers are associated with inflammatory bowel disease activity [9-12]. Other extraintestinal manifestations, such as uveitis and ankylosing spondylitis have an independent course with activity of IBD. And finally, the extraintestinal manifestations, such as primary sclerosing cholangitis (PSC) and pyoderma gangrenous may or may not be associated with the intestinal disease activity [9-12] (Table 2).

Table 1. *Prevalence of main extraintestinal manifestations (EIM) in patients with inflammatory bowel disease (IBD).*

Organ involved	Extraintestinal manifestation	Prevalence (%)*
Bone and joint	Peripheral arthropathy (Types 1 and 2)	4-20
	Axial Involvement (Spondylitis/ Sacroiliitis)	3-10
Skin	Erythema nodosum	10-20
	Pyoderma gangrenous	<1
	Oral aphthous ulcers	<1
	Sweet syndrome	<1
Eye	Uveitis	3-11
	Episcleritis	<1
	Scleritis	<1
Liver and biliary tract	Primary sclerosing cholangitis (PSC)	<1

Table 2. *Relationship between extraintestinal manifestations (EIM) and flare-ups of intestinal activity of inflammatory bowel disease (IBD).*

EIM associated with IBD activity
Type 1 peripheral arthropathy
Erythema nodosum
Episcleritis
Oral aphthous ulcers
EIM not associated with IBD activity
Type 2 peripheral arthropathy
Ankylosing spondylitis
Uveitis
EIM that may or may not be associated with IBD activity
Pyoderma gangrenosum
Primary sclerosing cholangitis (PSC)

Among patients with inflammatory bowel disease approximately one-third have at least one EIM lifelong and the risk of presenting at least one EIM, lifelong ranges from 6 to 47% [5-7,13]. History of perianal Crohn's disease, colonic involvement and smoking are related to increased susceptibility to the development of extraintestinal manifestations. The presence of prior MEI also appears to confer a greater probability of developing other extraintestinal manifestations [5-8,12-14].

The pathogenesis of extraintestinal manifestations in patients with IBD is not completely understood. Currently, the most accepted hypothesis is that the patient's gastrointestinal mucosa can trigger an immune response in extraintestinal sites, due to common epitopes in genetically susceptible individuals [15-17]. Table 3 summarizes the mechanisms involved in the pathogenesis of extraintestinal manifestations in IBD.

Objective

This review describes the clinical features and pathogenesis of the main extraintestinal manifestations in patients with IBD.

Literature Review

Bibliographical searches were performed in PubMed (January1990-October 2017), using the following key words: inflammatory bowel disease; ulcerative colitis (UC); Crohn's disease (CD); extraintestinal manifestations (EIM); musculoskeletal manifestations; cutaneous manifestations; ocular manifestations; hepatobiliary manifestations; pathogenesis of inflammatory bowel disease and pathogenesis of extraintestinal manifestations.

Reference lists from all available review articles, original articles and proceedings of major meetings were also considered and were restricted to articles in English only.

Musculoskeletal manifestations

Musculoskeletal involvement is the most common EIM observed in patients with IBD and is described in more than 30% of cases. The spectrum of these manifestations usually quite large, involving muscles, bones, tendons, joints and entheses, the latter being the most common involvement [18,19]. The articular manifestation most often described are inflammatory arthropathy, which are classically divided into two main groups; those that predominantly affects peripheral joints, i.e., peripheral arthritis and those which mainly affect the spine and therefore occur with spondylitis [12,18-20].

Peripheral arthropathy

Peripheral arthropathies occur in 5% to 20% of patients with inflammatory bowel disease, generally most common in Crohn's disease (CD) [18-20] and are subdivided into two groups: Type 1 or pauciarticular, usually affecting less than 5 large joints, such

as; knees, ankles, hips, elbows, wrists and shoulders. It relates to the activity of underlying IBD and related complications such as abscesses, perianal disease, or other EIM. There is usually little or no joint destruction, the pattern is asymmetric and migratory. Often self-limiting lasting a maximum of 10 weeks, but relapse is common and sometimes associated with uveitis and erythema nodosum [12,18,20]. The arthropathy Type 2 affects more than 5 small joints (polyarticular), showing a pattern of bilateral and symmetrical distribution. The metacarpophalangeal joint is most commonly involved. This type of joint disease characterized by chronic (lasting years) and its independent course of intestinal activity, and may even precede the onset of IBD. It is associated with uveitis, but has no association with erythema nodosum [12,18,20].

Axial arthropathies

Axial arthropathy occurs in 3% to 5% of patients with IBD and is more frequent in males. Axial arthropathy is usually categorized in ankylosing spondylitis and sacroiliitis. Patients with Crohn's disease are affected more often by this arthropathy (5%-22%) than patients with ulcerative colitis (2%-6%) [21]. Back pain and morning stiffness are the main symptoms of the axial arthropathies, which in contrast to the peripheral arthritis type 1, normally does not follow the course of the underlying IBD [7,12,22]. Therefore, the axial arthropathies can also precede the first intestinal symptoms of IBD. Most patients are HLA*-B27 positive [12,22]. The course of disease is generally progressive and often results in spinal destruction. Clinically, patients often have severe pain, which is usually compounded by the rest. Physical examination reveals limited spinal flexion (Schober test) and reduced chest expansion. Advanced cases are characterized by squaring of the vertebral bodies and bone proliferation and ankylosis, classically known as "bamboo spine". While the radiographs may show abnormal results, the column MRI is currently the gold standard for the diagnosis of ankylosing spondylitis, as senses inflammation prior to the onset of structural abnormalities and bone lesions. Different from ankylosing spondylitis, sacroiliitis is often asymptomatic and not progressive. Most patients with sacroiliitis are negative HLA-B27 and do not progress to ankylosing spondylitis, however, patients with radiographic findings of bilateral sacroiliitis are more likely to progress to ankylosing spondylitis [22,23].

Pathogenesis of musculoskeletal manifestations

The pathogenesis of musculoskeletal manifestations in patients with IBD is not fully understood. Currently, the most accepted hypothesis is the "gut-synovium axis" in which environmental and host factors act as triggers to trigger an inflammatory process in genetically predisposed individuals [24-26].

The intestinal bacterial flora seems to play a major role in this mechanism have been described an increasingly inappropriate activation of the immune system of the intestinal mucosa occurring with a dysregulation of the innate and adaptive immune responses directed against these bacteria or their products found in the intestinal lumen, and inadequate immune responses. This abnormal immune response can be facilitated by a dysfunction of intestinal epithelial barrier that

Table 3. Mechanisms related to the pathogenesis of extraintestinal manifestations in inflammatory bowel disease (IBD).

Mechanisms related to the pathogenesis of extraintestinal manifestations
Genetic susceptibility
Bacterial antigens and/or products found in the intestinal lumen
Imbalances of production and release of pro-inflammatory cytokines
Abnormal self-recognition against organ-specific cellular antigen(s)
Immunopathogenetic autoantibodies and immune complexes against organ-specific cellular antigen(s)

leads to increased permeability of mucous, facilitating the uptake of antigens and therefore their immune stimulation. In these cases, there appears to be a genetic predisposition to an imperfection of repair mechanisms and intestinal barrier integrity. Regarding the barrier dysfunction paper, it is known that the intestinal epithelium should act as a selective barrier to limit the penetration of antigens in the mucosa and generate responses of tolerance to commensal microorganisms and defense against pathogens. Consequently, the loss of intestinal barrier integrity, elicits an adaptive immune response, which is characterized by the activation of some immune cells, particularly dendritic cells and T cells and subsequent production of inflammatory cytokines, and prostaglandins and leukotrienes. Thus, the inflammatory response triggered by the loss of intestinal barrier integrity and consequent production and release of pro-inflammatory cytokines (TNF, IFNg and IL-13) and prostaglandins, may trigger joint damage due to common epitopes between intestinal bacteria and the synovium [15,16]. Another possible mechanism of pathogenesis of joint involvement in patients with IBD was demonstrated by the accession of intestinal lymphocytes activated in inflamed blood vessels in the synovium by multiple adhesion molecules and their receptors, of which the best known is the VAP-1 (Vascular adhesion protein 1) which supports the connection of multiple intestinal activated leukocytes [24,26,27].

The role of genetic factors has been implicated in the pathogenesis of IBD and its joint EIM. Among these are the most studied class I and II molecules of the major histocompatibility complex (HLA). In patients with IBD, some HLA alleles are associated with increased risk for the development of certain extraintestinal manifestations [28]. Peripheral arthritis type I is bound preferentially to HLA*-B35, while type II is associated mainly with HLA*-B44 [19,20]. HLA*-B27 shows a strong association with ankylosing spondylitis, present in about 50 to 90% of patients with DIIS, however HLA*-B27 not be related to IBD alone [19]. Another aspect of the genetic predisposition in IBD relates to mutations of *CARD15*/*NOD2* gene that were associated with Crohn's disease. The *NOD2* mutations can present with loss of control of the intestinal mucosal response to bacterial agents. One possible consequence may be the start of systemic responses that lead to uncontrolled inflammation. The prevalence of mutations in the *NOD2* gene in patients with Crohn's disease is seen in about 20 to 30% of cases in Western populations [29,30]. The results of studies showing an association between mutations in the *NOD2* gene with articular manifestations are controversial, being described in some series, association with sacroiliitis isolated and ankylosing spondylitis [31-33].

Another possible mechanism of common genetic predisposition to inflammatory bowel disease and ankylosing spondylitis concerns polymorphisms IL23R. Although its role is not fully understood, evidence suggests that the signaling pathways of IL23 play a key role in Th17 mediated inflammation, and may thus represent a common pathogenic mechanism in both IBD, as the ankylosing spondylitis [25,34,35].

Cutaneous manifestations

Cutaneous manifestations are common in patients with IBD and can occur in up to 15% of patients [8,12]. The most common cutaneous manifestations are: erythema nodosum, pyoderma gangrenosum and oral aphthous ulcers [8,10,12,36], but a broad spectrum of skin diseases may occur [12,41]. The diagnosis of cutaneous manifestations associated with IBD is based on their respective clinical characteristics and the exclusion of other diseases of the skin. Skin biopsy and other examinations are rarely necessary.

Erythema nodosum

Erythema nodosum is the most common dermatological manifestation in patients with inflammatory bowel disease (IBD), occurring in 3% to 10% of patients with ulcerative colitis and 4% to 15% of patients with Crohn's disease. A higher prevalence in female patients has been suggested [12,36-38]. Erythema nodosum is characterized by involvement of subcutaneous fat, usually presenting itself as painful subcutaneous nodules, red or violet staining, measuring from 1 to 5 cm in diameter and most commonly located on the extensor surfaces of the extremities, particularly on the tibial side previous.

Erythema nodosum presents association with intestinal activity of IBD, its course is self-limited and usually resolves itself without the formation of ulcers or scarring [5,37-39]. Often it is associated with joint involvement, ocular, with gangrenous pyoderma and isolated colonic disease [5,37,39-42].

When the nodules are biopsied, the lesion usually shows a focal panniculitis, but the diagnosis is most often clinical, and biopsy is only required in atypical cases (patients with no lesions on the legs, persistence beyond six to eight weeks, or development of ulceration) [12,39,43].

The appearance of the nodules is usually parallels with the intestinal activity, and rarely precede the onset of IBD, or occur in quiescent phases of the intestinal disease, treatment of IBD results in resolution of the cutaneous lesions [12,39,43].

Gangrenous pyoderma

The gangrenous pyoderma is the second most common dermatologic manifestation in patients with IBD, affecting between 0.1%-1.2% in Crohn's disease and ulcerative colitis 1%-5% [5,8,12,37,38]. The lesions are usually preceded by a trauma to the skin (even many years before) featuring a phenomenon known as pathergy. This trauma might even be minimal, such as a venipuncture. Pyoderma gangrenosum is a serious extraintestinal manifestations in patients with IBD. The lesions initially appear as erythematous papules, pustules single or multiple or that progresses rapidly to deep ulcers, painful with a central necrosis containing purulent material that is sterile culture unless secondary infections occur. These ulcers can be solitairy or multiple, unilateral or bilateral, and can range in size from several centimeters to an entire lib [12,41-43]. The most commonly affected sites include the extensor surfaces of the legs, but can develop in any area of the body, including the abdominal wall adjacent to the stoma after colectomy or surgical scars [5,12,36,40,41].

Patients with severe disease involving the colon are more likely to develop these dermatologic complications, biopsy of the lesions, usually reveals a sterile abscess [41-43]. The course of

the disease is unpredictable and has no association with intestinal activity of IBD [36,40,41], and there have been conflicting data regarding the distribution of gangrenous pyoderma among Crohn's disease and ulcerative colitis, but appears to be more common in ulcerative colitis [12,41-43].

The oral cavity is often affected in patients with IBD. Periodontitis and other injuries, such as aphthous stomatitis and, in more severe cases, vegetating pyostomatitis are found in up to 10% of patients with IBD. Oral lesions are more common in CD compared with UC and more prevalent in males, and also more frequent in the upper gastrointestinal tract CD and perianal involvement [44-46]. Painful lesions of aphthous stomatitis are usually located in the buccal and labial mucosa, tongue and oropharynx and present relationship with the underlying IBD activity. Usually intestinal symptoms precede the oral manifestations, but 5% to 10% of oral lesions affected patients may precede the intestinal picture [44-46]. Pyostomatitis vegetans manifests as multiple pustular sometimes hemorrhagic eruptions anywhere on the oral mucosa with a cobblestone pattern, the treatment includes antiseptic mouthwashes and topical steroids [44-46].

Sweet syndrome

Sweet syndrome, or acute febrile neutrophilic dermatosis is a rare dermatologic inflammatory disorder associated with IBD and others systemic disease such as malignancy, characterized by the abrupt appearance of painful, swollen and erythematous papules, plaques, or nodules on the skin, generally involving the arm, legs, trunk, hands or face [12,43,47,48]. The syndrome may also present some systemic manifestations such as arthritis, fever, and ocular symptoms (conjunctivitis). Its activity is usually parallels with the gastrointestinal disease, but may precede the diagnosis of IBD. Most cases respond to topical or systemic corticosteroid therapy and heal without scarring [12,43,47,48].

Pathogenesis of cutaneous manifestations

Similarly, to other extraintestinal manifestations, pathogenesis of cutaneous manifestations in patients with IBD is not fully understood. In regard to erythema nodosum, the precise pathogenic mechanism is not completely understood. It is believed to occur a hypersensitivity reaction that leads to the immune complexes deposit in small blood vessels and connective tissue adjacent to the subcutaneous fat [45,46]. The pathogenesis of erythema nodosum as extraintestinal manifestation of IBD is due to an abnormal immune response, releasing cytokines (TNFα, IFNγ and IL17), directed against common epitopes between intestinal bacteria and skin [47-49].

The pathogenesis of gangrenous pyoderma, as well as erythema nodosum, is not fully understood. It is believed that there may be a decrease of cellular immunity characterized by abnormal T cell response associated with dysfunction of neutrophils plus an overexpression of proinflammatory cytokines such as IL-8, IL-16, IL-17 and TNF-α [45,46,50-52]. The pathogenesis of pyoderma gangrenosum in IBD is proposed to be the result of an abnormal immune response to self-cross-reactive antibodies directed to epitopes common in the gut and skin [50,52,53].

Associations between the major histocompatibility complex and cutaneous manifestations of IBD have been evidenced. An association between erythema nodosum and HLA-B*15 was previously shown [54]. In more recent study identified a new gene, TRAF3IP2, which appears to be involved in susceptibility to both erythema nodosum, as the gangrenous pyoderma. This gene appears to be involved in encoding proteins that modulate humoral immunity, particularly IL-17. This aspect demonstrates the presence of a pathogenic mechanism common to both major cutaneous manifestations associated with the IBD [52,55].

Ocular manifestations

The incidence of ocular manifestation in patients with inflammatory bowel diseases has been reported to range 2-5%, and is often associated with joint involvement. They are the third more common extraintestinal manifestation, occurring more frequently in CD patients (3.5%-6.3%) than patients with UC (1.6%-4.6%) [6,8,56-59]. Usually the ocular manifestations are of inflammatory origin, and is more common in patients with colitis or ileocolitis affection than in patients with isolated small-bowel disease, this difference in incidence is explained by an immune complex hypersensitivity reaction to a colonic antigen [6,8,56-59]. However, some of these manifestations may reflect the overall activity of the underlying inflammatory bowel disease. The main ocular manifestations include; episcleritis, scleritis and anterior uveitis [6,8,56,57].

Episcleritis and scleritis

Episcleritis is inflammation of episcleritis, the layer directly below the conjunctiva, characterized by episcleral, sectoral or diffuse injection, unilateral or bilateral. It is more common in Crohn disease than in Ulcerative Colitis, manifests as painless hyperemia and there is no loss of vision or photophobia. This event is the most common ocular manifestation, occurring in 2%-5% of patients. It occurs in parallel with the activity of intestinal disease [56,58]. Scleritis affects the deeper layers of the eye, and can cause visual impairment if not diagnosed early. The presentation may be similar to episcleritis, patients often complain of severe pain associated with tenderness to palpation [57-59]. In case of impairment of vision, scleritis must be suspected, it is mandatory aggressive treatment, and prompt referral to an ophthalmologist. Recurrent scleritis can lead to scleromalacia, retinal detachment, or optic nerve swelling [57-59]. Treatment is based in systemic steroids or immunosuppressants, and control of the underlying bowel disease [57-59].

Uveitis

Uveitis is less common than episcleritis occurring within 0.5 to 3% of patients with IBD, but on the other hand, can have potentially serious consequences. Uveitis may precede the diagnosis of IBD and can be associated with dermatologic manifestation axial and/or peripheral arthropathy. It is not related to the intestinal disease activity, being more common in women and ulcerative colitis compared to Crohn's disease. This event is presented as hyperemia, photophobia, headache and blurred vision [56-60]. Classically, the eye exhibits a ciliary flush, in with the redness is most intense in the center and radiates outward with diminishing intensity [57-60].

Evaluation via a slit lamp is mandatory, and treatment may include topical and systemic steroids to prevent permanent loss of vision [57-60].

Pathogenesis of ocular manifestation

In its pathogenesis, the ocular manifestations in the context of IBD are usually of inflammatory origin. HLA Association studies in patients with ulcerative colitis showed that the HLA-DRB1*0103 correlates with articular and ophthalmic manifestations. In turn, the uveitis appears to be associated with the HLA-B*27, HLA*B58 and HLADRB1*0103 [28,56,60]. This genetic predisposition to an environmental trigger, such as a less dirty environment and microorganisms lead to loss of intestinal barrier integrity triggering an abnormal immune response that leads to T cell activation and consequent Th1 or Th2 response directed against extraintestinal tissues, who share similar epitopes or microvasculature, in this case, the environment or the intraocular tissues [15,16,48,61].

The pattern of immune response triggered and the strong association between HLA-B*27 and HLA-DRB1*0103 with enteropathic arthropathy, mainly axial arthropathy, explain the reasons why the ocular manifestations often occur in association with the joint commitment [20,54,56,60].

Hepatobiliary manifestations

Hepatobiliary manifestations are common in the context of IBD, may be present in more than 50% of patients during the course of the disease [13]. Primary sclerosing cholangitis (PSC) is the most common manifestation hepatobiliary in patients with IBD, however other hepatobiliary events such as; gallstones, hepatotoxicity by medications, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and portal vein thrombosis represent other liver and biliary manifestations found in association with inflammatory bowel disease [13,62,63].

Primary sclerosing cholangitis

The primary sclerosing cholangitis (PSC) is a relatively common extraintestinal manifestation in patients with IBD, being present at 1.4 to 7.5% of these patients. It occurs most commonly in association with UC compared to DC are found in up to 2.4 to 7.5% of UC patients. Moreover, approximately 80% of patients with PSC have concomitant diagnosis of a IBD usually with UC [64]. Although there is an association between UC and the PSC there is no relationship of this with the onset, duration or activity IBD [63,64].

The PSC is a cholestatic chronic and irreversible disease characterized by progressive inflammation of the bile ducts intrahepatic and extrahepatic, resulting in fibrosis of the biliary system and later in a secondary biliary cirrhosis, which can lead to liver failure and/or cholangiocarcinoma. PSC is the greatest risk factor for developing cholangiocarcinoma, occurring in approximately 12%-15% of patients undergoing liver transplantation for PSC [63,65]. The clinical picture is characterized by symptoms such as fatigue, weight loss, itching, jaundice, and abdominal pain. Laboratory manifests itself as a chronic cholestatic disease; with elevations of alkaline phosphatase, gamma glutamyl transferase and bilirubin and aminotransferases usually within the normal range [65].

The diagnosis is usually made by magnetic resonance imaging of the biliary tract [66], which are evidenced dilatation and diffuse stenosis and multificais, affecting both intra bile ducts and extrahepatic, giving the appearance of "rosary account" [65,66]. Liver biopsy is usually indicated only in cases where there is a suspected PSC of small ducts, since it rarely provides diagnostic PSC. The classic findings of the PSC found on liver biopsy are ductopenia and a fibrous obliteration of the bile ducts giving the appearance of "onion skin" [62,65].

Pathogenesis of primary sclerosing cholangitis

The exact etiologic mechanism of PSC remains unknown to date. Immunological, genetic and environmental factors together seem to be involved in its pathogenesis.

A possible autoimmune mechanism has been suggested, since autoantibodies, such as; p-ANCA (cytoplasmic perinuclear anti-neutrophil antibody), antinuclear antibodies (ANA) and anti-smooth muscle may be present in some cases of PSC, especially when in association with UC. Another aspect that speaks in favor of the participation of immune mechanisms in the pathogenesis of PSC is the fact that both the PSC, as the IBD are immune-mediated diseases [67,68].

Similarly, to other EIM an association between genes of the major histocompatibility complex (HLA) and the PSC has been demonstrated. A higher prevalence of PSC has been observed in first-degree relatives of patients with PSC and UC, strengthening the role of genetic predisposition in the pathogenesis of these diseases [69]. Some HLA genes, such as; HLA-B8, HLA-DRB1*0301(DR3), HLA DRB3*0101(DRw52a), and HLA-DRB1*0401(DR4) were associated with an increased susceptibility to PSC and UC [70,71]. Furthermore, some genetic locus for susceptibility to UC, such as REL, CARD9 and IL2 were also associated with zip code, once again demonstrating the role of genetic predisposition in the context of these pathologies [72].

Thus, the most widely accepted hypothesis, regarding the pathogenic mechanisms of the CEP, is that genetically predisposed individuals, when exposed to an environmental agent have an abnormal immune response, which ultimately leads to the development of the disease.

Discussion and Conclusion

The extraintestinal manifestations are common in patients with inflammatory bowel disease, occurring in approximately one third of these. They can affect a number of organs and systems, and the gastrointestinal tract, demonstrating that both Crohn's disease, ulcerative colitis as are systemic disease whose manifestations and consequences are not restricted only to the intestine. Some of these EIM, as the type I arthropathy and erythema nodosum are associated with the activity of the bowel disease and others like PSC and ankylosing spondylitis follow an independent course of the underlying IBD activity.

Its pathogenesis, although not fully understood, is believed to be the result of a complex interaction between an aberrant adaptive immune response directed against extraintestinal sites due to common epitopes in consequence of the loss of intestinal barrier integrity in individuals genetically predisposed. A

better understanding and further advances in knowledge of the mechanisms involved in the pathogenesis of MEI in patients with IBD are of fundamental importance to ensure an appropriate diagnosis and management of these conditions, which can often be even more debilitating than the actual inflammatory bowel disease. Further studies in this field are needed.

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