APMB - Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Medico Biologiche
Vol. 108(1) 2020

ISSN 1828-6550

DOI: 10.6092 / 1828-6550 / APMB. 108.1.2020. SD2

Scholarly Dialogs SD2 (1-12)

Extra-intestinal manifestations in inflammatory bowel disease.

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Abstract

Extraintestinal manifestations (EIMs) in patients with inflammatory bowel diseases (IBD) are immuno-mediated conditions that may occur in up to 50% of IBD patients. Several organ systems may be involved such as joints, skin, liver, and eyes. EIMs may occur before or after the diagnosis of IBD but the pathogenic mechanisms are still poorly defined. Some of them such as peripheral arthritis, erythema nodosum, aphthous stomatitis, episcleritis, and uveitis are associated to IBD activity and are responsive to IBD-therapies while others like pyoderma gangrenosum, axial spondylarthropathy or primary sclerosing cholangitis follow an independent course and require specific treatments. The present review provides an overview on the classification of the main groups of EIMs occurring in IBD patients.

KeyWords: Crohn's disease, ulcerative colitis, spondiloarthropathies, episcleritis, uveitis, pyoderma gangrenosum

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This Review article is based on the Lecture in memoriam of Gaetano Barresi Professor of Pathology

Introduction

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and Ulcerative colitis (UC), are chronic systemic inflammatory disorders affecting the gastrointestinal (GI) tract. Their pathogenesis is the result of a complex interaction between genetic and environmental factors together with a dysregulation of the innate and adaptive immune response (1,2). IBD patients may suffer from extraintestinal manifestations (EIMs), inflammatory conditions that may involve different organs and systems with an important impact on morbidity and quality of life (3,4).

In this short review we provide an overview on the main groups of EIMs from prevalence, pathogenesis, diagnosis, to patient management.

Classification.

Classification of EIMs depends on their pathogenesis (immunomediated or secondary to systemic inflammation) and their relationship with intestinal disease activity. Immunomediated EIMs may occur before or after the diagnosis of IBD. The association with intestinal activity justifies their classification into EIMs specifically associated with IBD

activity like peripheral arthritis, erythema nodosum (EN), aphthous stomatitis, episcleritis, and uveitis usually responsive to IBD-therapies or into manifestations with an independent disease course, e.g. pyoderma gangrenosum (PG), axial spondylarthropathy, uveitis, or primary sclerosing cholangitis that require specific treatments. A summary of this classification is shown in the Table 1.

Tab 1. Classification of EIMs in relation to IBD activity and organ systems.

	Organ	Disease
Associated with intestinal activity	Musculoskeletal system	Peripheral spondyloarthritis
	Eyes	Episcleritis Uveitis
	Skin	Erythema nodosum Stomatitis Sweet syndrome
Not associated with intestinal activity	Musculoskeletal system	Axial spondyloarthritis
	Skin	Pyoderma gangrenosum
	Hepatobiliary system	Primary sclerosing cholangitis

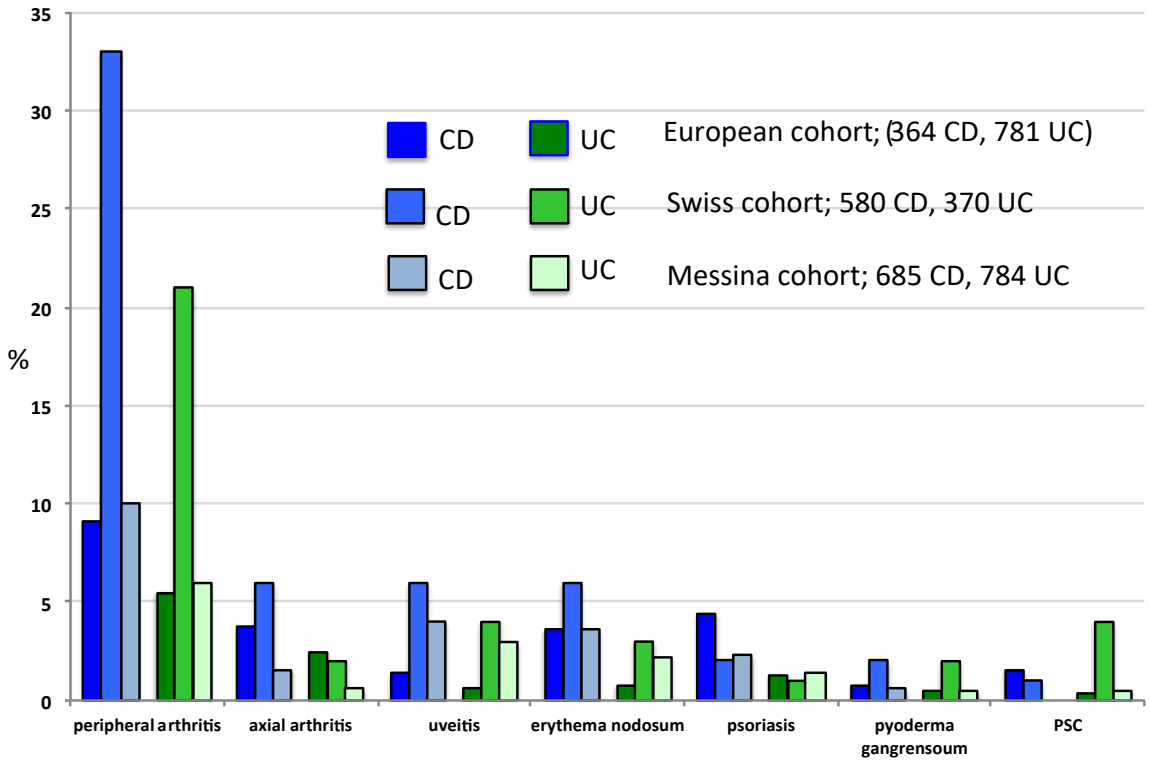
In some reports pathologies secondary to IBD, i.e. mainly due to systemic inflammation or to an alteration of the absorptive function of the intestine are frequently also mentioned as EIM such as gallstones, urinary stone disease, venous thromboembolism, and osteoporosis (4) but these events are not considered in the present review. From the University of Manitoba IBD epidemiology database (UMIBDED) we know that several other pathologies, e.g. anaemia, asthma, psoriasis, demyelinating diseases, nephritis, pulmonary disease, cerebrovascular disease, and pericarditis were found with an increased frequency in IBD patients compared with controls (5). Very recently, a new classification has been proposed categorizing EIMs in 1. extraintestinal manifestations due to multifocal inflammation, e.g. spondyloarthritides, uveitis, episcleritis, Sweet syndrome, pyoderma gangrenosum, erythema nodosum, etc, 2. Complications of IBD and its treatment, e.g. metabolic bone disease (steroids), cataracts (steroids), drug-induced skin disease (anti-TNF, thiopurines), lung fibrosis (methotrexate), interstitial nephritis (mesalazine), etc, and 3. Associated conditions with uncertain mechanisms, e.g non-inflammatory arthralgias, asthma, psoriasis, vitiligo, etc (6).

Epidemiology.

The prevalence of EIMs varies between population-based investigations (7) and referral centre-

based reports (8) being more frequent in the latter. In previous studies about 6 - 47% of IBD patients experience at least one EIM with peripheral spondiloarthritis being the most common manifestation, and 27% experience a second EIM. (9-12) More recent data by Vavricka et al. (8) reported in a large nationwide Swiss cohort of IBD patients the occurrence of EIMs in 43% of CD patients and 31 % of UC patients, respectively, with a preponderance in women (50%). In figure 1, the rates of most frequently occurring EIMs are represented in an European population-based cohort (7), a report based on Swiss referral centres (8), and the frequency observed in patients followed at our centre in Messina. It appears that in the Swiss study peripheral arthritis occurs 2 – 3 times more frequently compared to the other cohorts, however, this difference is due to the inclusion of arthralgias in the group of definite arthritis.

Fig. 1 Representation of different rates of the most frequently occurring EIMs in an European population-based cohort (7), in a study based on Swiss referral centres (8), and the frequency observed in patients followed at our centre in Messina. CD: Crohn's disease; UC: ulcerative colitis; PSC: primary sclerosing cholangitis.



With the exception of primary sclerosing cholangitis (PSC), EIMs occur more frequently in CD compared with UC, but, while in CD disease location seems not to influence frequency of EIMs, in UC they present more frequently in extensive colitis compared with ulcerative proctitis (7).

Data on the chronological appearance of IBD-related EIMs show that in up to 25% of patients they may occur before the diagnosis with a median time of 5 months (range 0-25 months). In the other

75% of patients, the diagnosis of the first EIM was made after IBD diagnosis with a median time of 92 months (range 29-183 months) (9). Moreover, patients may suffer from a combination of different EIMs with an increased risk to develop other manifestations with or after the occurrence of the first one (3,10).

Higher rates of anaemia and lower rates of osteopenia are reported in paediatric onset IBD, whereas in CD, early disease onset was associated with higher rates of aphthous stomatitis compared to higher rates of ankylosing spondylitis and PSC in paediatric-onset UC (11). Finally, compared with elderly-onset IBD, EIMs are definitely more frequent in paediatric IBD (12).

Pathogenesis and genetics.

The pathogenic mechanisms underlying the development of EIM are still poorly understood. Different hypotheses have been proposed to explain the occurrence of EIMs such as the expansion of the inflammatory response from bowel to other sites through different mechanisms while other consider EIMs as independent inflammatory events.

According the aforementioned categorization proposed by Hedin et al (6), an extension of the immune response outside the intestine may lead to the ectopic expression of the Mucosal Vascular Addressin Cell Adhesion Molecule-1 (MAdCAM-1) and chemokine ligand 25 (CCL25) in the portal tract (13, 14). Other mechanisms may involve T cell trafficking influenced by non gut-specific adhesion molecules leading to binding of leukocytes to the synovial membrane thus evoking low-grade inflammation and injury (15). Translocation of gut microbial antigens together with inflammation-induced alterations of hepatic tight junctions may represent the base for IBD-associated hepatic manifestations (16, 17), whereas cross-reactivity between gut bacteria antigens and HLA molecules are believed to be of key importance in the pathogenesis of HLA-B27-associated joint inflammation (18). Finally, circulating antibodies may bind to epitopes commonly expressed in the intestinal mucosa and in other tissues (19, 20).

On the other hand, EIM may be explained as independent inflammatory events through a shift in the "inflammatory tone" (21) or due to systemic changes in the innate immune function (22). Gut microbial-driven distant inflammatory events through an increased intestinal permeability together with an alteration of haematopoiesis have also been discussed. (6)Probably all of these hypothesized pathogenic factors are not mutually exclusive and may contribute to the occurrence or EIMs.

Finally,EIMs may also be explained as independent inflammatory events due to common risk factors such as genetics or environmental factors, e.g. smoking. (23,24) Concerning genetics, there is evidence of a positive family history for several immune-mediated diseases in patients with IBD in (25, 26) Several human leukocyte antigen (HLA) alleles show a strong association with specific EIMs, e.g. HLA-B8/DR3 in PSC and ulcerative colitis. Another well-studied genetic risk factor is

HLA-B27 that is associated with joint inflammation (mainly axial spondyloarthropathy and type 1 arthritis) together with skin and eye manifestations; despite this association, HLA-B27 seems not increase the risk for IBD. (27-29) The most common HLA genotypes associated with EIMs are summarized in table 2. Other genetic factors have also been described such as the mutations of the CARD15 gene witch encodes the well-known protein NOD2, a risk factor for CD. Studies on polymorphisms identified an association of NOD2 with sacroiliitis, uveitis and with a fibrostenotic behaviour of CD, whereas in UC an association of the HLA DRB1*0103 allele with extensive disease and RIMs was described (30,31).

Joint manifestations.

Articular involvement, known also as spondyloarthritides (SpAs), represent the most common and, frequently, the first EIM to appear in IBD patients. SpAs are diagnosed in about 15% - 27% of IBD leading to a significant burden for patients (3,32,33). Based on clinical presentation and symptoms, SpAs are classified in peripheral arthropathies and axial arthropathies. SpAs must be distinguished from other upcoming issues namely arthralgia (pain without signs of inflammation) and fibromyalgia. The former entity may reach up to 20% of IBD patients, especially CD patients, whereas the frequency of the later is still under debate(34).

Tab 2. Summary of principal HLA genotypes associated with different EIMs. EIMs: Extra intestinal manifestations; CD: Crohn's disease; UC: Ulcerative colitis. (ref 8,27,28,30,33,59,60)

HLA	EIM
HLA-B27	Joint (Spondylarthropathy) skin and eyes
HLA-B8/DR3	Primary sclerosing cholangitis
HLA-B58 HLA-DRB1*0103	Joint, skin and eyes
HLA-B35	Pauciarticular peripheral arthritis
HLA-B44	Polyarticular peripheral arthritis
HLA-A2 HLA-DR1 HLA-DQw5	Increased risk of EIMs in general in CD patients
HLA-DR103 HLA-B58 HLA-B27	Increased risk of EIMs in general in UC patients

Peripheral arthropathies.

Prevalence of peripheral arthropathies ranges from 5 to 20% with a preponderance in CD. Peripheral arthropathies usually are negative for rheumatoid factor or anti-nuclear antibodies (ANA) and show a less destructive course than axial forms without signs of erosions or deformity at radiographic imaging (3).They are classified, according to clinical manifestations, into oligoarticular and polyarticular peripheral arthritis or type 1 or type 2 respectively (35). Type 1 arthritis is characterized by an involvement of less than 5 joints, usually starting in large joints as knee or ankle (the most commonly involved) and migrating asymmetrically to other large joints such as wrist, elbow, or shoulders. (36) This subgroup of SpA is often self-limiting (usually symptoms last for less than 10 weeks) without a persistent damage and is associated with IBD flare. Type 2 arthritis are characterized by an involvement of more than 5 joints that start with a symmetrical distribution pattern involving smaller joints, mainly metacarpophalangeal joints. Unlike type 1, this type of arthropaties can persist also several years and is unrelated to IBD activity. (35)

Axial arthropathies.

Axial spondyloarthritis include ankylosing spondylitis (AS) and sacroiliitis and occurs in 5-22% of patients with Crohn's disease and 2-6% of UC patients (33). Diagnosis is based on the main symptoms that are the back pain and morning stiffness and radiological evidence of sacroiliitis. The gold standard for radiological diagnosis is magnetic resonance imaging (MRI)for the detection of inflammation or progression of damage. Axial SpAs follow an independent disease course from IBD and diagnosis often precedes that of bowel disease. The frequency of AS is about 4% or less as reported in previous studies while the diagnosis of IBD in patients with AS occurs in about 5-10% of patients. (8, 33, 37) As described above, genetic susceptibility include the presence of HLA-B27 positivity in up to 90% of patients with idiopathic AS and in 25-33% of patients with AS and IBD. (38)

Treatment.

Treatment strategies are related to specific EIM. Peripheral arthropathies respond to treatment of IBD as corticosteroids during flare for short term relief. Other options are non-steroidal anti-inflammatory agents and local steroid injections. In several studies, sulfasalazine in IBD patients with symptomatic peripheral arthropathiesrepesent an effective option although in other studies efficacy seems to be modest or not superior to placebo (39). Data on efficacy of immunomodulators in peripheral arthropathies (methotrexate, 6MP, and azathioprine) are scarce while TNF-α inhibitors have proven efficacy for both arthropathies and IBD not responsive to conventional treatment (40,41). In AS the first therapeutic approach are

nonsteroidal anti-inflammatory drugs (NSAIDs) or Cox2 inhibitors that are considered safer with respectto concomitant IBD. In patients intolerant or unresponsive to this approach, biologics, e.g. anti-TNFα, represent the best option (40). There is also growing evidence of a positive effect of Vedolizumab, an anti-integrin α4β7 antibody, despite its gut-specific action (42,43).

Eye manifestations.

Ocular manifestations are reported in 4-11% of patients with IBD, most frequently in CD (8). The most common is episcleritis followed by uveitis. Depending on the site of involvement, uveitis is subclassified in anterior (iritis), intermediate (vitritis), posterior (choroiditis) or panuveitis. The most common form is anterior uveitis while intermediate or posterior uveitis and scleritis are rare and more aggressive and, if untreated, may lead to blindness (44).

In episcleritis and scleritis inflammation is confined to episclera and sclera, respectively, and clinical presentation includes acute hyperaemia and burning. Clinical course of episcleritis and scleritis is associated to IBD activity unlike uveitis that follows an independent disease course (45). While episcleritis has less symptoms and a more benign course, uveitis it is characterized by pain, photophobia, blurred vision and headache. A prompt diagnosis is essential to start treatment and avoid severe complications as loss of vision. Regarding treatment, steroids, immunomodulators, and anti-TNFα are effective in treating ocular manifestations together with topical treatment (46).

Mucocutaneous manifestations.

Mucocutaneous EIMs are common in IBD patients and are subclassified into skin manifestations (erythema nodosum, pyoderma gangrenosum, Sweet syndrome) that are more common and mucosal manifestations as aphthous stomatitis, more frequent in paediatric onset IBD. Other class of skin manifestations in IBD patients are specific manifestations as metastatic CD or related to specific IBD therapy as psoriasis, eczematous eruptions and the lupus-like syndrome induced by anti-TNFα (47).

Skin manifestations.

Erythema nodosum.

Erythema nodosum (EN) is the most common skin manifestation in IBD and is reported more frequently in CD with a frequency of 15% and a female preponderance (47). The pathogenesis is unknown but a delayed type IV hypersensitivity reaction as pathogenic mechanism has been proposed (48). Clinical presentation usually occurs after IBD diagnosis and is characterized by raised, erythematous, red-violet, and typically painful nodules of 1–5 cm in size. The most commonly affected areas are extensor pretibial skin while other less frequent locations are the trunk

or upper extremities (47). Diagnosis is based on clinics and biopsy is required only in case of atypical presentation. EN activity is associated with IBD activity however severity of EN is independent from severity of intestinal inflammation. Treatment with corticosteroids, immunomodulators, or anti-TNFα is usually effective.

Pyoderma gangrenosum.

Pyoderma gangrenosum (PG) is less common than EN but is more severe and disabling. This manifestation is more frequent in UC patients but prevalence is low ranging from 0.4 to 2% (8,47).

PG is frequently preceded by trauma (the pathergy phenomenon) (49) and its pathogenesis is still unclear. An abnormal neutrophil function and impaired cellular immunity seems to be involved.(50) As clinical presentation, PG is characterized by a rapid development of a skin pustule evolvinginto deep ulceration of 2–20 cm in diameter with a purulent but sterile discharge (3). The typical site of onset are peristomal skin or lower limbs but can occur also in other parts of the body and may be accompanied by other symptoms such as fever and arthralgia. Diagnosis is clinical and biopsy is performed only to rule out other skin disorders. However, biopsy shows in early phase perivascular lymphocytic infiltrate or neutrophilic predominance with ulceration and abscess in a late phase. (3). Treatment consists in systemic steroids as first line treatment, followed by Cyclosporine or anti-TNFα. (51-53)

Sweet syndrome.

Sweet syndrome is an acute febrile neutrophilic dermatosis presenting as painful nodules or pustules often associated with fever and arthralgia. The prevalent site of onset are the upper limbs and typically it is associated with the exacerbation of underlying diseases such as malignancy, infections, infections, or inflammatory disorders. Topical or systemic corticosteroids are effective as first line treatment (47).

Mucosal manifestations.

Oral manifestation as aphthous stomatitis or the less frequent pyostomatitis vegetans occur in up to 10% of IBD patients and are more frequent in CD (48). The most common oral manifestation is aphthous stomatitis. This manifestation is characterized by painful ulcers of the oral mucosa, tongue, and oropharynx and follows IBD activity with response to specific treatment along with topical antiseptics or steroids.

Hepatic manifestations.

Primary sclerosing cholangitis (PSC)

PSC is one of the most common EIM of IBD. Is a chronic cholestatic disease characterized by progressive inflammation ad successive fibrosis with the formation of strictures of the intra- and extrahepatic bile ducts. It occurs in 4%–5% of IBD patients but IBD is diagnosed in up to

80% of patients with PSC, this confirms a close association between the two entities (54,55). PSC is diagnosed mainly in UC patients with extensive disease and with rectal sparing and the increased risk of colorectal cancer in this setting of patients deserves closer endoscopic surveillance (every 1-2 years) (56). As well as an increased risk of colorectal cancer, there is an increased risk of cholangiocarcinoma with a bad prognosis and other complications such as cholangitis. Clinical features include itching, fever, abdominal pain, fatigue, and other unspecific symptoms. Serological findings include cholestasis and autoantibodies that are positive in about 65-88% of patients. (57) The gold standard for diagnosis is magnetic resonance cholangiography to detect strictures in bile ducts. Treatment options are scarce and no drugcan prevent fibrotic evolution of PSC. Ursodeoxycholic acid (UDCA) has been used to reduce abnormal levels of liver enzymes but efficacy in preventing disease progression has not been demonstrated, so the only current option is liver transplantation (58).

Conclusions.

EIMs are frequent in IBD patients. These conditions can occur at different time-points during the natural history of IBD and significantly influence morbidity. An early diagnosis and treatment are essential in preventing complications. Gastroenterologists needs for multidisciplinary approach for the management of these patients in order to prevent disability and optimize treatment.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant

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Communicated and received Sept. 9, 2019, revised and accepted March 8, 2020 published on line June 15, 2020