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Review

INFLAMMATORY BOWEL DISEASE AND EXTRAINTESTINAL MANIFESTATIONS

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ABSTRACT

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, are chronic and recurrent inflammatory diseases. Although the typical symptoms are localized in the gastrointestinal tract, there are also extraintestinal manifestations (EIMs) associated with IBD, probably caused by immune reactions secondary to the pathology of origin. Anybody can be affected by EIMs, which can be dermatological, pulmonary, ocular, musculoskeletal, hepatobiliary and neurological, et al. This represents a therapeutic challenge for clinicians, who must first establish a diagnostic and then a multidisciplinary therapeutic path, in order to guarantee an optimal quality of life for the patient.

1. Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of unknown etiology including Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD is multifactorial and involves the alteration of the intestinal microbiota, alteration of the immune response, genetic alterations and environmental factors such as stress, use of drugs, and cigarette smoking (1-3). Symptoms of IBD involve the entire gastrointestinal tract in CD and the last tract of the intestine, the colorectal, in UC, and include symptoms such as diarrhea, abdominal pain, rectal bleeding, fatigue and weight loss (4 -8). Patients with IBD, furthermore, often require immune-modifying treatment, which could increase the risk of opportunistic infection (9,10).

In addition to the classic gastrointestinal symptoms, IBDs can be associated with extraintestinal manifestations (EIMs). It is estimated that up to 40% of patients with IBD can have EIMs and sometimes the clinical spectrum of EIMs is very broad, sometimes manifesting more severe than IBD itself (11).

The etiopathogenesis of EIMs is not yet known but many extraintestinal manifestations are thought to be secondary to immune reactions. It is believed that the inflamed gastrointestinal mucosa can trigger immune responses at the extraintestinal site due to shared epitopes, for example, of intestinal bacteria (12). This would mean that bacteria that are translocated across the permeable intestinal barrier trigger an adaptive immune response that is ultimately unable to discriminate between bacterial epitopes and epitopes from other areas of the body (12,13). Associations of EIMs in IBD with major histocompatibility complex loci such as HLA-A2, HLA-DR1 and HLA-DQw5 in patients with CD and the HLA-DR103 genotype in patients with CU have also been demonstrated. Particular HLA complexes have also been linked to specific EIMs. HLA-B8 / DR3 is associated with an increased risk of primary sclerosing cholangitis in UC, while HLA-DRB1 * 0103, HLA-B * 27 and HLA-B * 58 are associated with EIM of joints, skin and eyes, respectively, in patients with IBD (10).

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In this article we want to focus attention on EIMs in reference to specific target organs: dermis, lung, eye, nervous system, musculoskeletal and hepatobiliary systems.

2. Dermatological manifestations

Cutaneous manifestations of IBD occur in 15% of patients (12,13), in particular we find them in 22-75% of patients with CD and in 5-11% of patients with UC. About 10% of these manifestations are present at the time of IBD diagnosis. However, a large variety of skin lesions can develop over the course of the disease. (11,14)

Based on their pathophysiological association with the underlying disease (CD or UC), skin manifestations are classified into

- specifications
- reactive
- secondary to malabsorption / malnutrition, and;
- secondary to treatment (14).

Specific manifestations can show the same histopathological changes as IBD (11). These manifestations are the result of the spread of the intestinal inflammatory process in the skin and / or external mucosa. They are represented by continuous and / or contiguous lesions, including perianal / peristomal ulcers, orofacial lesions, and metastatic lesions, defined as noncaseous granulomas and dermal infiltrates with multinucleated giant cells, lymphocytes, plasma cells and eosinophils in locations distant from the gastrointestinal tract (16). Non-caseous granulomas occur only in patients with CD, as CU lesions do not extend to external mucosal surfaces and include fistulas, abscesses, fissures and ulcers (14,16). Perianal CD was found in 36% of patients with CD (11). Approximately 25-80% of these patients are adults, and commonly present with perianal fistulas and abscesses. Other features can include anal fissures, perianal strictures, and fecal incontinence (14). Oral CD occurs in approximately 8-9% of patients with CD and is generally considered an extension of enteric granulomatous lesions, characterized primarily by angular cheilitis, lip ulcers, gingival or mucous nodules, and cracked lower lip. Aphthous stomatitis is more common in patients with CD, but recurrent aphthous stomatitis is more common in patients with UC. Differences in presentation of oral lesions can be found between CD and CU: CD is characterized by both specific and non-specific oral lesions, while only nonspecific ones are found in UC. In CD, oral lesions are defined specific if histopathological data show evidence of granulomas (similar to those observed endoscopically in the intestine) (14,17). Specific lesions include indurated tag-like lesions, pebbles, mucogingivitis, lip swelling, deep linear ulcerations, and midline labial fissuring (18). Metastatic CD, also defined by the term "non-contiguous cutaneous CD", is characterized by the formation of cutaneous granulomas in sites distant from the gastrointestinal tract (14).

Reactive manifestations do not share the same histopathological findings but share common pathogenetic mechanisms.

The lesions are thought to occur as a result of an altered immune response to common pathogenic flora in the skin and intestines (11).

The most commonly encountered are erythema nodosum, more common in patients with CD (4-15%) than in patients with UC (3-10%), characterized by raised, tender, red or purple subcutaneous nodules between 1 and 5 cm and occurs mainly on the anterior portion of the lower limbs, and gangrenous pyoderma (PG), which is the most severe and debilitating skin manifestation and occurs in 1-3% of IBD cases (1-10% of patients with CD and 0.5-20% of patients with UC).

It can occur anywhere in the body, but the most common sites are the legs and peristomal sites, and the most common clinical manifestations are ulcerative and pustular (11,114).

Skin manifestations due to malnutrition or malabsorption include diseases secondary to vitamin and trace element deficiency. In the case of IBD, malabsorption and malnutrition are two very common conditions due to lesions involving both the oral cavity and the intestinal tract responsible for absorption (4-8).

Skin manifestations associated with malabsorption / malnutrition are summarized in Figure 1.

Finally, the secondary manifestations associated with the treatment are the result of immune-mediated adverse reactions to the treatment of IBD and are a direct consequence of the therapies adopted. This is a relatively new phenomenon that can occur with any type of anti-TNF treatment and is not associated with the underlying activity of IBD (11,15).

Nutritional deficiency	Skin manifestation
Vitamin A	Phryynoderma
Vitamin B12; iron	Stomatitis-glossitis-angular cheilitis
Vitamin C	Scurvy
Vitamin E	Seborrheic dermatitis; seborrheic edema
Vitamin K	Ecchymosis and petechiae
Essential fatty acids	Dry skin; eczema
Amino acids and proteins	Hypopigmentation of the hair; glossitis; nail abnormalities
Zinc	Enteropathic acrodermatitis

Figure 1. Skin manifestations associated with malnutrition / malabsorption in IBD

3. Pulmonary manifestations

The airways are less commonly involved and therefore often neglected. As a result, respiratory tract involvement in patients with inflammatory bowel disease is believed to be underestimated. The pathogenesis is believed to be multifactorial, involving the common embryological origin shared by the respiratory and luminal digestive tract, molecular mimicry, and immunological interactions leading to the deposition of immune complexes in the affected tissue. The spectrum of airway manifestations related to inflammatory bowel disease is broad. Not only does it include direct involvement of the airways (i.e. airways, interstitium and pleura), but it can also result as a consequence of systemic involvement such as in thromboembolic events.

Furthermore, it can also be related to other conditions affecting the respiratory tract such as sarcoidosis and alpha-1 antitrypsin deficiency (19).

IBD EIMs have been implicated in all anatomical sites of the lung tree and include inflammation of the airways of the bronchi and bronchioles (bronchiolitis, bronchiectasis, chronic bronchitis and granulomatous bronchiolitis) and parenchymal inflammation (such as organized pneumonia, interstitial pneumonia, lymphocytes interstitial pneumonia, eosinophilic pneumonia and granulomatous interstitial lung disease) (20,21).

Bronchial inflammation and suppuration are the most common manifestations of pulmonary involvement in IBD and include chronic bronchitis and bronchiectasis in which bronchial dilation is seen on chest x-ray or CT (20,22). Involvement of the respiratory system in IBD, which can range from a simple defect in lung function without symptoms, to a fibrosing alveolitis with an increased risk of mortality, is relatively rare but sometimes potentially harmful (20). Imaging studies in patients with IBD have shown varying degrees of results such as an accidental finding of bilateral opacities and infiltrates in an asymptomatic patient, scattered and poorly defined nodules with cavitation on high-resolution computed tomography (HRCT). Radiologically, some patients showed bilaterally nodular infiltrates, some showed diffuse infiltrates, and some showed a mass. Bronchoscopy and thoracoscopy showed a diffuse pulmonary appearance and a picture of interstitial pneumonia with granulomatous changes with or without abscesses and necrotic debris. In another study of lung biopsies from IBD patients who had been on mesalamine for years, they showed chronic bronchiolitis with non-necrotizing granulomatous lesions, organized pneumonia with focal granulomatous features, and interstitial pneumonia with rare giant cells (20). The most prevalent results on pulmonary function tests (PFTs) were a decrease in forced expiratory volume in 1 s, forced expiratory flow, FEV1 / FVC and transfer coefficient for carbon monoxide (Dlco), Dlco / alveolar volume (23). Treatment strategies for these associated pulmonary symptoms depend on the model or part of the involvement. Steroids, in general, have been shown to significantly decrease both the extent and severity of symptoms (24).

4. Ocular manifestations

The incidence of ocular complications in IBD ranges from 4 to 10%, and occurs more often in CD than in CU (23). Ocular manifestations of IBD include conjunctivitis, episcleritis, scleritis, marginal keratitis, anterior uveitis, retinitis, retinal vascular occlusive disease, optic neuritis, and orbital inflammatory disease (25,26).

Among ocular EIMs, episcleritis is the most common ocular manifestation of IBD. Clinical presentation includes episcleral, sectoral, or diffuse injection, which pales with topical application of phenylephrine and tenderness on palpation. There is no loss of vision, change in the pupillary response to light, involvement of the cornea, blurred vision or photosensitivity (photophobia). Mild to moderate pain and mild tenderness on palpation are typical. Episcleritis is associated with active CD and can be considered an indicator of active bowel disease (26).

Corneal disease (keratopathy) is a rare manifestation of IBD, but if it occurs the patient will experience pain in the eyes, foreign body sensation, irritation and, very occasionally, decreased vision. If it occurs in isolation, there will be no eye redness or pupillary changes. IBD-associated keratopathy presents as a subepithelial keratopathy and occurs bilaterally and symmetrically with infiltrates located 2 to 3 mm within the corneoscleral limbus. They tend not to cause visual morbidity because the lesions typically spare the central visual axis. Patients usually present with a known diagnosis of IBD but rarely keratopathy may precede the diagnosis (25).

Another ocular EIM is uveitis, an inflammation of the uveal tract, the middle layer of the eye, which includes the iris, the ciliary body and the choroid (13,27). In UC patients, uveitis was found in 3.5% of patients with inactive disease and 4.1% of patients with active disease. Uveitis in IBD patients is initially treated with corticosteroid-based eye drops. If unsuccessful, systemic steroids, immunosuppressants, or anti-TNF agents can be used (13).

Corticosteroids are first-line therapy for most ocular complications of IBD that do not respond to treatment of an IBD flare-up or occur regardless of general disease status. If refractory to topical treatment, systemic corticosteroids should be considered for severe ocular inflammation. Systemic NSAIDs may also be considered, although these increase the risk of exacerbation of underlying IBD. Cytotoxic immunosuppressive agents such as azathioprine may also be considered. These agents may be particularly effective in patients who are HLA-B27 positive (25,26).

5. Neurological manifestations

The incidence of neurological complications in IBD ranges from 0.25% to 47.5%. The pathophysiology of the neurological manifestations of IBD is predominantly immune-mediated, but dysfunctions of the brain-gut axis, arterial and venous thromboembolism, infections, nutritional deficiencies and side effects of drugs (steroids, metronidazole, sulfasalazine, anti-TNF-α, anti-integrin antibodies) are other contributing mechanisms. IBD patients have an increased risk of arterial and venous stroke, mainly during periods of flare-ups. Vasculitis is extremely rare (28). The neurological EIMs most commonly associated with IBD are summarized in Figure 2.

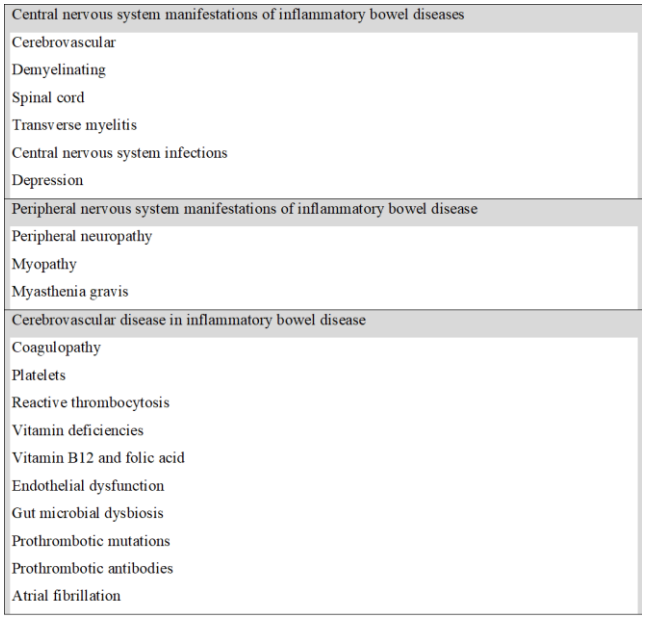

Figure 2. Neurological complications of inflammatory bowel disease (modified by Ferro et al. 2021 Ref. 28)

6. Muscle - skeletal system manifestations

Musculoskeletal EIMs represent the most common manifestation of IBD and involve 6% to 46% of patients, depending on the clinical and / or skeletal radiological criteria used (29).

Among the musculoskeletal manifestations we have:

- Peripheral arthritis in 5-14% of patients with UC and in 10-20% of patients with CD. The diagnosis is mainly clinical, based on the evidence of an objective inflammation of the peripheral joints, with typical signs of arthritis, enthesitis, tenosynovitis and bursitis. The classic form is characterized by asymmetrical oligoarticular arthritis involving fewer than five joints, preferably involving the large joints. This arthropathy usually involves self-limiting acute attacks lasting less than 10 weeks, is strongly associated with dermatologic EIMs such as erythema nodosum and uveitis, and is indicative of active IBD (13).
- Spondyloarthropathy (SA), which can occur in conjunction with peripheral involvement including synovitis, dactylitis and enthesopathy such as yarrow tendonitis, plantar fasciitis and chest wall pain. Although there is a strong association with HLA-B27 in idiopathic AS (over 90% of cases), the association with HLA-B27 in spondylitis that complicates IBD is lower (13).
- Sacroiliitis, usually bilateral, can be asymptomatic or symptomatic. Asymptomatic sacroiliitis is observed in up to 50% of patients with CD. Symptomatic sacroiliitis is characterized by lower back / buttock pain after rest (13).

Management of intestinal inflammation is an important therapeutic goal because it can also induce remission or reduction of activity for musculoskeletal manifestations. However, in a considerable proportion of patients, more often those with polyarticular diseases, despite the improvement or disappearance of intestinal inflammation, joint disease persists (13).

7. Hepato - biliary manifestations

Among the hepatobiliary EIMs, primary sclerosing cholangitis (PSC) represents the most important and most frequent, so much so that in 60-80% of patients with PSC there is an underlying IBD (28). PSC is found with a prevalence of up to 5% in patients with UC and less frequently in patients with CD (11). Risk factors for developing PSC in UC patients are male sex, pancolitis in UC patients, non-smoker at diagnosis, and a history of appendectomy (31). Histologically, PSC is characterized by the infiltration of lymphocytes into the intrahepatic and extrahepatic biliary tree followed by an inflammatory process that triggers fibrosis, which can eventually lead to stenosis of the small or large bile ducts. This may be followed in the long term by liver cirrhosis, end-stage liver disease and cholangiocarcinoma. Importantly, PSC is associated with a tenfold increased risk for developing colorectal cancer in patients with IBD (32).

In addition to PSC, liver EIMs include autoimmune hepatitis (AIH), IgG4-related cholangitis, and granulomatous hepatitis. In addition, there are multiple treatments for IBD that can affect the liver and cause hepatitis (thiopurine, methotrexate, anti-TNF antibodies and JAK inhibitors among others). Furthermore, immunosuppression can lead to a reactivation of hepatitis B or cause hepatitis mediated by other viruses such as CMV, EBV, and others (13).

8. Conclusions

EIMs in IBD represent a major therapeutic challenge as they can affect any organ or tissue and worsen the quality of life of patients with CD or UC. The association between EIMs and IBD is frequent in both treated and untreated subjects and represents a clinical challenge for doctors who find themselves having to treat not only symptoms related to IBD but also those related to EIMs. The correct approach involves a basic multidisciplinary assessment, with the establishment of a team consisting of gastroenterologists, endoscopists, dermatologists, ophthalmologists, neurologists and orthopedists, for proper management of the problem.

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