A Review of Extraintestinal Manifestations and Complications of Inflammatory Bowel Disease

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Abstract
Extraintestinal manifestations (EIMs) are common in inflammatory bowel disease (IBD), affecting about 5%–50% of the patients. In addition, about 29% of EIM cumulative incidence occurs after 15 years of disease duration; in some cases, they may even occur before the diagnosis of IBD. However, there is currently lack of prospective studies assessing EIM rates of IBD using adequate diagnostic criteria. Family history of IBD is a predisposing factor as well as the occurrence of one EIM predisposes to others. In terms of the clinical course, EIMs such as peripheral arthritis, oral aphthous ulcers, erythema nodosum (EN) and episcleritis have a temporary association with IBD activity, while others such as axial arthropathy, pyoderma gangrenosum (PG), primary sclerosing cholangitis (PSC) and uveitis have an independent disease course. This review would summarize the most common EIMs, their prevalence and the suggested management.

Keywords: Extraintestinal manifestations, inflammatory bowel disease, arthritis, osteoporosis, erythema nodosum, primary sclerosing cholangitis

INTRODUCTION
Extraintestinal manifestations (EIMs) are common in inflammatory bowel disease (IBD), affecting about 5%–50% of the patients. In addition, about 29% of EIM cumulative incidence occurs after 15 years of disease duration; in some cases, they may even occur before the diagnosis of IBD. However, there is currently lack of prospective studies assessing EIM rates of IBD using adequate diagnostic criteria. Family history of IBD is a predisposing factor as well as the occurrence of one EIM predisposes to others. In terms of the clinical course, EIMs such as peripheral arthritis, oral aphthous ulcers, erythema nodosum (EN) and episcleritis have a temporary association with IBD activity, while others such as axial arthropathy, pyoderma gangrenosum (PG), primary sclerosing cholangitis (PSC) and uveitis have an independent disease course.

ARTHROPATHY
Arthropathy is common among IBD patients, and these disorders are known as spondyloarthritis (SpA). SpA is further classified as axial and peripheral based on the primary symptoms. A diagnosis of axial SpA is made based on radiographic findings of sacroiliitis associated with inflammatory low back pain. Notably, radiologic findings of sacroiliitis are observed in about 15%–27% of IBD patients, whereas progressive ankylosing spondylitis (AS) with syndesmophytes occurs in only about 3%–10% of the patients. In addition, in Crohn’s disease (CD) and AS patients, HLA-B27 is found in about 25%–75% of cases, whereas in those with...
isolated sacroilitis, HLA-B27 is found in only 7%–15% of cases. HLA-B27 positivity in patients with IBD indicates that these patients are at a higher risk of developing AS, however, because HLA-B27 positivity is considerably lower in idiopathic AS patients, it cannot be considered as a diagnostic marker.\[6,10\]

Peripheral SpA in IBD patients is an inflammatory arthropathy that usually does not cause bone erosion or deformity, unlike psoriatic arthritis and other inflammatory arthropathies. Orchard et al. classified IBD-related peripheral arthropathies into two categories based on articular distribution and natural history. Type 1 is defined as pain in five joints or lesser along with swelling or effusion, mainly in the large weight-bearing joints of the lower extremities. The symptoms persist for <10 weeks and are correlated with IBD flares. The symptoms are typically acute and self-limiting but do not cause permanent joint damage. In contrast, in Type 2, more than five joints are affected, with a symmetric distribution, and mainly affect joints in the upper limbs. In this type, the symptoms can persist for months or years, independent of the IBD activity, without causing erosion or deformity. The differential diagnosis of arthropathy is arthralgia, corticosteroid-induced osteonecrosis and infliximab-induced lupus-like syndrome. Arthralgia, which is joint pain in the absence of inflammation, is also common in IBD. It may be due to an initial adverse reaction associated with thiopurine therapy or due to the withdrawal of corticosteroids.

IBD-associated dactylitis and enthesopathies have been investigated less extensively. Enthesitis is frequent, characterized by the inflammation of the tendon insertion and may lead to bone erosion and proliferation. Its symptoms are characterized by severe pain, swelling and tenderness. Dactylitis, also called sausage-like fingers or toes, is a characteristic and highly specific feature of SpA, occurring in 2%–4% of IBD patients.\[9,13\]

The presence of peripheral arthritis is more common in CD, particularly in the presence of colonic disease, and is mostly asymmetrical and oligoarticular. Further, it often coincides with, or presents after, the appearance of IBD, with a prevalence of 5%–20% (5%–14% in ulcerative colitis [UC] and 10%–20% in CD patients), but occasionally may also precede the symptoms of IBD.\[13,34\]

In general, peripheral arthritis has good prognosis, whereas that of axial involvement is less favorable and not related to the clinical activity of IBD. Rather, it is linked with the prognosis of AS, which is usually a progressive condition that has direct impact on the patients’ quality of life. Therefore, it is important to identify axial SpA early before its progresses to the radiographic stage. This progression occurs in about 10%–20% of the cases in the initial 2 years of follow-up, mostly in those with an elevated C-reactive protein level or active inflammation on magnetic resonance imaging.\[13\]

In terms of treatment, there are no prospective controlled trials in patients with IBD-associated arthropathy, and most recommendations are based on the findings in SpA alone, mainly AS. According to these recommendations, patients with axial SpA should be jointly managed by gastroenterologist and rheumatologists because of the possible debilitating disease course, and intensive physiotherapy and nonsteroidal anti-inflammatory drugs (NSAIDs) are the preferred treatment options. Although long-term use of NSAIDs should be avoided in IBD, short-term use has been found to be well-tolerated.\[10\]

In patients with intolerance, unresponsiveness or poor response to NSAIDs, anti-tumor necrosis factor (TNF) therapy is the preferred treatment, as methotrexate and thiopurines have limited efficacy. Long-term effects of anti-TNF agents on radiographic progression of lesions are yet to be ascertained; nonetheless, recent data suggest potential efficacy of this therapy on the progression of early SpA, such as less pronounced bone formations.\[18–21\]

In general, peripheral arthritis is treated by effective treatment of the underlying IBD. For symptomatic relief, short-term treatment with systemic corticosteroids, nonsteroidal anti-inflammatory agents and local steroid injections can be adopted. Methotrexate and azathioprine are considered minimally effective in the treatment of peripheral arthropathy. In terms of sulfasalazine, a Cochrane review by Chen and Liu found that it has modest efficacy in treating patients with peripheral arthropathy, especially in those with shorter disease duration and increased erythrocyte sedimentation rate. In contrast, a systematic review by van den Berg et al. concluded that the effect of sulfasalazine on disease activity was not superior to placebo. Nonetheless, in cases of persistent arthritis, sulfasalazine has been shown to have a beneficial effect in large joint arthropathies. Anti-TNF therapy is recommended in resistant cases, while oral corticosteroids may be effective for short-term relief. For arthralgia, symptomatic therapy with simple analgesia is usually effective.

**METABOLIC BONE DISEASE**

In IBD patients, low bone mass and osteoporosis are common, affecting about 20%–50% of the male and
female patients. Factors that contribute to this are chronic inflammation, treatment with corticosteroids, extensive small bowel disease or resection, smoking, age, lack of physical activity and nutritional deficiencies. In adults, a diagnosis of osteoporosis is made when the bone mineral density (BMD) T-score is ≤2.5 on dual-energy X-ray absorptiometry. Several longitudinal studies have found a T-score of <2.5 in 5%–37% of IBD patients.

Screening recommendations for IBD patients are similar to that for the general population and are based on risk factors such as postmenopausal state, age, ongoing corticosteroid treatment, cumulative treatment with corticosteroid for more than 3 months and history of low-trauma fractures. In osteoporotic patients, the risk of vertebral fractures increases dramatically; however, studies have also documented vertebral fractures in patients with a normal bone density. Therefore, osteoporosis may not be the primary risk factor for vertebral fractures in IBD patients. In the majority of IBD patients, who are primarily young adults aged 20–40 years, the lumbar spine BMD has been found to be significantly reduced.

Studies have demonstrated that being in a state of stable remission for 3 years helps to normalize the bone density of IBD patients. Treatment with anti-TNF agents may improve bone density due to the reduction of chronic inflammation. The immunologic role of vitamin D has been studied and IBD has also been implicated as a cause for its deficiency, however, as vitamin D deficiency is also commonly noted in newly diagnosed IBD patients, it is likely that it directly contributes to increased IBD risk, in addition to its effect on bone metabolism.

**EYE DISEASES**

The most common ocular manifestations of IBD are anterior uveitis and episcleritis. In contrast, scleritis and intermediate/posterior uveitis are extremely rare (<1%), but if left undiagnosed and untreated, their progression can cause permanent visual impairment. The progress of episcleritis is parallel to IBD activity, whereas the progress of uveitis is not associated with the disease activity and also occasionally precedes its onset. Vascular occlusion likely secondary to vasculitis (including central retinal artery occlusion), orbital inflammation and anterior ischemic optic neuropathy are some of the other rare ocular manifestations of IBD with potentially severe consequences. It should be noted that ocular manifestation is found in 4%–12% of IBD cases, although a prevalence rate of up to 29% has also been reported. Episcleritis is usually painless and is characterized by hyperemic sclera and conjunctiva, with occasional occurrence of itching and burning. Uveitis is comparatively less common but has more severe symptoms such as blurred vision, eye pain, photophobia and headache. If not managed, uveitis can lead to permanent loss of vision, and thus the attending gastroenterologist should promptly refer these patients to an experienced ophthalmologist.

Episcleritis can often be differentiated from scleritis based on having mild pain (caused by hyperemia of the conjunctiva and episcleral) and no visual changes. However, the occurrence of photophobia, visual disturbance and moderate-to-severe pain should prompt ophthalmic referral.

With regards to the management, dry eyes can be treated with topical lubricants. For treating episcleritis, the underlying IBD symptoms should be managed, and additional topical NSAIDs and glucocorticoids may be used. For treating anterior uveitis, topical corticosteroids and cycloplegics should be used. However, there is limited evidence available regarding the treatment of refractory uveitis and other rare manifestations. Studies have shown treatment to have higher efficacy in uveitis patients without IBD. Nonetheless, in some case series, topical and systemic corticosteroids, immunomodulator therapy or biologics have been shown to have favorable responses. Based on the experience in patients without IBD, in posterior uveitis and scleritis, expert opinion favors the use of immunomodulators and biologics such as azathioprine, methotrexate, infliximab and adalimumab.

**SKIN DISEASES**

**Erythema nodosum**

EN is characterized by the occurrence of raised, tender, red or violet subcutaneous nodules (1–5 cm in diameter), making it easily diagnosed. The extensor surface of the extremities, particularly the anterior tibial areas, are the most commonly affected areas, and occasionally, the trunk or upper extremities are also involved. EN is often associated with other systemic symptoms including arthralgia and fatigue. It can be diagnosed clinically by excluding metastatic CD, and biopsy is usually not performed. EN is the most common dermatologic manifestation in IBD patients and is more common in females and patients with CD (4%–15% CD vs. 3%–10% UC cases). In general, EN is associated with IBD activity and flares, but not with its severity. Owing to its association with disease activity, treating the underlying IBD is the mainstay of treatment. However, in severe cases, treatment with systemic corticosteroids may...
be required, while in resistant cases or those of frequent relapses, management with infliximab, azathioprine or adalimumab may be required\[^{51,52}\]

**Pyoderma gangrenosum**

PG is characterized by the appearance of a skin pustule that rapidly becomes a burrowing ulcer with violaceous edges, about 2–20 cm in diameter. PG most commonly occurs on the shins and adjacent to stomas, although it can occur anywhere on the body, including genitalia. It initially appears as a single or multiple erythematous papule(s)/pustule(s), but subsequent necrosis of the dermis leads to the development of deep excavating chronic ulcerations. In PG, the histopathological findings are nonspecific, and thus its diagnosis is made after excluding other likely skin diseases based on the characteristic findings of the lesions. In some cases, a biopsy from the periphery of the lesion may be required to exclude specific skin diseases. Therefore, a high index of suspicion is required to avoid misdiagnosis of PG.\[^{49}\]

In general, PG develops more frequently in UC than CD patients,\[^{46,47,53,54}\] and it is often preceded by trauma (pathergy).\[^{65}\] PG course can be associated with IBD activity or be independent, which is especially the case in UC patients. PG reoccurs in about one-fourth of all cases after treatment, generally in the same site as the initial lesion.\[^{46}\]

In terms of treating PG, owing to its debilitating nature, immunosuppressive drugs are mainly used for a rapid recovery. Conventionally, especially in the dermatologic experience, systemic corticosteroids and cyclosporine are the most commonly used drugs.\[^{56,58}\] However, since the availability of infliximab, PG management in UC patients has changed. In a multicenter, randomized, placebo-controlled trial for the treatment of PG with infliximab,\[^{59}\] the response rate was found to be >90% in patients with PG for <12 weeks, and 50% in those with PG for >12 weeks. A few case series have shown adalimumab to be effective in treating PG.\[^{60,62}\]

**PRIMARY SCLEROSING CHOLANGITIS**

Altered biochemical liver tests may be present in up to 30% of the patients with IBD,\[^{63}\] and PSC is one of the most common causes for these findings.\[^{64}\] In fact, PSC is the most common IBD-associated liver disease\[^{65}\] and can affect up to 4%–5% of IBD patients.\[^{66,67}\] Findings of bile duct strictures have also been reported in IBD patients with normal liver function tests.\[^{68}\] In Caucasian populations, about 70%–80% of PSC patients have concurrent IBD,\[^{65}\] more frequently in UC than CD patients.\[^{69}\]

The primary symptoms of PSC are pruritus, malaise, fever, chills, night sweats and pain in the right upper abdominal quadrant; however, they are mostly intermittent. PSC often presents asymptptomatically, and thus a high degree of suspicion is required. In patients with cholestasis, a diagnosis of PSC can be made with magnetic resonance cholangiography after other secondary causes of sclerosing cholangitis have been excluded.\[^{70,74}\]

In about 5%–10% of patients, magnetic resonance cholangiography findings are normal despite the histopathological changes being consistent with that found in PSC; this variant is now defined as “small-duct PSC,”\[^{75}\] and is usually associated with a better prognosis.\[^{76}\] The histopathological changes of PSC are typically patchy, and thus liver histology in the early phase may be completely normal.\[^{77}\]

The diagnosis of PSC in IBD dramatically impacts the prognosis because of possible complications such as cholestasis, steatorrhea, cholangitis, cholecystolithiasis, cholangiocarcinoma, colorectal carcinoma, osteoporosis and vitamin deficiency. PSC is also frequently associated with other autoimmune diseases such as Hashimoto’s thyroiditis, celiac disease and type 1 diabetes. More importantly, in patients with IBD and concurrent PSC, the rate of colorectal carcinoma is significantly higher than that in IBD patients without PSC or normal controls, and thus requires more frequent monitoring.\[^{78,79}\]

Currently, no treatment options have shown strong and consistent evidence of altering the disease course.\[^{80}\] Medium dose of ursodeoxycholic acid (15–20 mg/day) is no longer used by most clinicians due to its limited ability to only improve liver function parameters and not the disease course.\[^{81}\] In addition, high-dose ursodeoxycholic acid (28–30 mg/day) are contraindicated because it increases the risk of colorectal cancer.\[^{82}\] Liver transplantation is the only available therapy, and its 5-year survival rates are about 85%.\[^{83,84}\] In patients with PSC, it is crucial to investigate and recognize complications such as strictures and cholangiocarcinoma.

**OTHER MANIFESTATIONS**

There are several other rare and heterogeneous manifestations and complications of IBD that should be taken into account and carefully investigated, such as portal vein thrombosis (occurring in about 1% of the cases)\[^{85}\] and hepatic amyloidosis (0.9% in CD and 0.07% in UC patients).\[^{86}\] In addition, two specific types of acute pancreatitis associated to IBD have been
described. In the first type, the pathogenic pathways are presumed to be similar to that of IBD. This type comprises idiopathic, autoimmune and granulomatous pancreatitis as well as pancreatitis associated with PSC. The second type is mostly caused by adverse events in the management of IBD, mainly through use of thiopurines. This type comprises drug-induced and biliary pancreatitis as well as pancreatitis secondary to duodenal CD.\[87\]

In terms of neurological manifestations in IBD, the prevalence varies widely from 3% to 39%.\[88\] However, the data available do not provide strong evidence of prevalence rates owing to lack of population-based studies and the reported studies having the small sample size and referral bias. A wide range of neuropathies have been described, such as demyelinating, small- and large-fiber sensory, and sensorimotor neuropathies. In peripheral neuropathy, only about one-thirds of the patients have a disease course related to IBD activity. Neuropathies affecting the central nervous system comprise cranial neuropathies, optic neuritis, ophthalmodiplegia and hearing loss. In terms of treatment, there is a lack of recommendations available. However, in patients with a history of demyelination, anti-TNF use is contraindicated, as it is associated with episodes of demyelination.\[89\]

In Western populations, a modest increase in IBD-associated risk of arterial thromboembolism has been reported,\[88,91\] specifically ischemic heart disease, stroke and mesenteric ischemia. The cause of this is likely because of chronic systemic inflammation in IBD patients, which predisposes to atherosclerosis.\[92\] In terms of bronchopulmonary involvement in IBD, the exact prevalence remains unknown.\[93\] However, pulmonary function tests are frequently abnormal in IBD patients, with discovery of latent interstitial pulmonary involvement in 20%–55% of cases. The abnormalities include ventilatory defects, bronchial hyperresponsiveness, sputum or bronchoalveolar lavage lymphocytosis as well as histologic and radiologic abnormalities.\[94,93\]

In addition, IBD-associated interstitial pneumonia has also been described, and it includes nonspecific and usual interstitial pneumonia as well as hypersensitivity interstitial, lymphocytic interstitial, eosinophilic interstitial and organizing pneumonias.\[96\] Finally, IBD patients, particularly those with CD, have a high frequency of kidney stones due to uric acid or calcium oxalate.\[97\] In addition, rare cases of tubulointerstitial and granulomatous interstitial nephritis as well as IgA nephropathy have been reported.\[98\]

CONCLUSIONS

EIMs are relatively common throughout the IBD course, and in some cases, can occur even before the diagnosis of IBD. Therefore, clinicians should maintain a high index of suspicion, as early diagnosis and management of EIMs can help reduce the overall morbidity. A multidisciplinary approach may be required for managing IBD and the involved organs, especially in case of the more uncommon EIMs. In several cases, managing the underlying IBD activity can also help in controlling the EIM; however, an unmet need remains due to lack of controlled trials.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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