

Extraintestinal Manifestations of Inflammatory Bowel Disease

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ABSTRACT

Inflammatory bowel disease (IBD) is primarily a disease of the digestive tract system, though it may affect other organ systems outside of the intestines. Extraintestinal manifestations (EIMs) can occur in up to one third of patients with Crohn's disease or ulcerative colitis. The most common EIMs involve dermatologic and musculoskeletal manifestations. EIMs may either parallel intestinal inflammation or be completely independent of disease activity. Physicians should be aware of EIMs and think systematically when evaluating patients with IBD, as nearly every organ can be involved, and a multidisciplinary treatment approach should be undertaken to improve outcomes and quality of life.

KEYWORDS: inflammatory bowel disease; extra intestinal manifestations; Crohn's disease; ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic immune-mediated diseases of the gastrointestinal tract. The chronic inflammation is a result of a dysregulated immune response that leads to tissue inflammation and destruction. However, IBD should not solely be regarded as an intestinal disorder, but rather a systemic disease given that a significant number of patients will develop extraintestinal manifestations (EIMs). Between 25-40% of patients with IBD¹ will develop EIMs and the presence of one confers the risk to develop subsequent EIMs. Rarely, up to five organ systems have been reported to be impacted at one time. Most patients who develop EIMs will do so after a diagnosis of IBD has been established. However, about 25% of patients will be diagnosed with an EIM initially, prior to uncovering a diagnosis of IBD. In a large IBD cohort study, the most common EIMs diagnosed prior to the onset of IBD included peripheral arthritis or axial arthritis, uveitis, and primary sclerosing cholangitis (PSC).² Risk factors that have been strongly correlated with the development of EIMs include cigarette smoking, colonic disease, and perianal CD.³ Extraintestinal symptoms may involve virtually any organ system with a potential for a profound impact on the patient's quality of life, in some instances more so than bowel disease. The most affected systems

are the skin, musculoskeletal, and eyes, but several other organs may also be affected, including the kidneys, blood, and hepatobiliary.

The pathogenesis of EIMs in IBD is not clearly elucidated. The European Crohn's and Colitis Foundation working group has defined the mechanism for EIMs to better standardize for scientific discovery and research as the following: "An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."⁴ Genetics, environmental triggers, and the intestinal microbiota have been postulated as potential culprits for the development of EIMs. Studies have demonstrated overlaps between genetic risk loci for IBD and EIMs and found a concordance for EIMs in parent-offspring pairs and sibling-pairs of 70% and 84% respectively.⁵ The most well-known genetic risk factor for central arthritis (Ankylosing spondylitis) in association with IBD is HLA-B27 positivity. Tobacco use has been shown to be associated with a higher risk for development of both skin and joint EIMs.⁶ The role of the intestinal microbiota in the pathogenesis of IBD is well established as an undesired and overacted immune response is directed at the intestinal flora. One of the hypothesized processes in which the microbiota plays a role in the development of EIMs is in part through molecular mimicry. Cross-reactivity of the immune system against other extra-intestinal sites occurs due to gut microbiota antigens sharing similar epitopes present on cells in organs. Another potential etiology of inflammation developing beyond the intestine may be attributed to loss of the intestinal barrier integrity, which then allows for bacterial flora and its components to translocate to distant sites and lead to an inflammatory response. The importance of the colonic microbiota in inflammation is seen in the findings that patients with IBD that involves inflammation of the colon develop EIMs at a higher rate compared to those with isolated small bowel disease.

It is important to differentiate EIMs from extraintestinal complications. EIMs are immune-mediated conditions which echo the immunologic mechanisms of inflammation in bowel disease, whereas extraintestinal complications (**Table 1, see Appendix**) arise from secondary processes that are direct

Table 2. Extra-Intestinal Manifestations and Association with Bowel Disease Activity

EIM	Parallels Bowel Disease Activity	Unclear Association With Disease Activity	Independent of Bowel Disease Activity	Therapy
Oral • Aphthous Stomatitis • Pyostomatitis Vegetans	✓ ✓			Treatment of intestinal inflammation
Ocular • Episcleritis • Scleritis • Uveitis	✓		✓ ✓	Refer to Table 3
Musculoskeletal Peripheral Arthritis • Type 1 (<5 joints) • Type 2 (≥5 joints) Axial Arthritis • Ankylosing Spondylitis • Sacroiliitis	✓		✓ ✓ ✓	Treatment of intestinal inflammation COX-2 inhibitors Sulfasalazine (notably in UC) Anti-TNF
Dermatologic • Erythema Nodosum • Pyoderma Gangrenosum • Sweet's Syndrome • Bowel associated dermatosis and arthritis syndrome (BADAS)	✓ ✓ ✓	✓		Treatment of intestinal inflammation Local • Wound care, Topical steroids, topical calcineurin inhibitors Extensive • Systemic steroids, systemic cyclosporine, Anti-TNF ³⁰ , methotrexate, azathioprine, Dapsone ³¹ , minocycline, IVIG ³² Treatment of intestinal inflammation Short course of systemic steroids if needed
Hepatobiliary • Primary sclerosing cholangitis			✓	Close monitoring and surveillance given strong malignancy association (cholangiocarcinoma, HCC, colon cancer, gallbladder cancer) Liver Transplantation for cirrhosis

or indirect sequela of bowel damage (anemia, nephrolithiasis, Vitamin B12 deficiency) or related to medications used to manage the disease.⁷ EIMs can manifest in parallel with IBD disease activity or be completely independent (Table 2), sometimes being even more difficult to manage and treat than the bowel disease itself. Patient awareness through education and a multidisciplinary team approach are important key factors for early identification and treatment of EIMs that can lead to symptom resolution and improving quality of life.

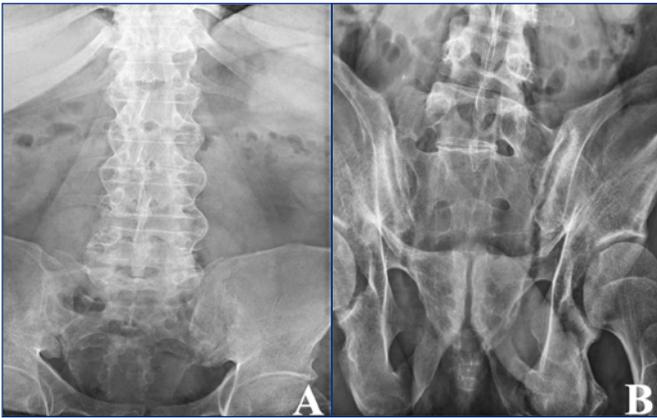
MUSCULOSKELETAL

Musculoskeletal symptoms represent the most common EIMs in IBD and are termed “seronegative spondyloarthropathies.” Peripheral small and large joints as well as axial joints may be affected in up to 40% of patients with IBD.⁸ Musculoskeletal EIMs can precede, occur concurrently, or develop following the diagnosis of IBD, often by as many as 10 years.⁹ Males and females are equally affected, but patients with colonic disease are more impacted than those

with isolated small-bowel disease.

Peripheral arthritis is a migratory arthritis that shows little to no joint deformity, but inflammation may last up to several weeks. Peripheral arthropathy is divided into two types: type 1 and type 2. Type 1 is pauciarticular (typically involving fewer than 5 joints), seronegative, asymmetric and will often parallel disease activity. Joints that may be affected include the knees (most common), shoulders, hips, wrist, ankles, and elbows. Type 2 is polyarticular (involving 5 or more joints), symmetric, is independent of bowel disease, and typically affects the metacarpophalangeal joint. Type 2 is associated with an increased risk of uveitis.¹⁰ The diagnosis of type 1 and type 2 is based on clinical suspicion, as imaging is unrevealing due to the lack of joint destruction. Treatment for type 1 is based on addressing bowel disease whereas type 2 is more directed at symptoms with rest, intra-articular steroid injections, physiotherapy, or sulfasalazine. The selective COX-2 inhibitor, celecoxib, has been demonstrated to be a potential treatment option and used with caution in patients with IBD since it is not been found to be associated with inducing flares.^{11,12}

Figure 1. (A) Ankylosing Spondylitis. (B) Sacroiliitis.



Axial arthropathies occur less frequently than peripheral arthritis and includes both ankylosing spondylitis and sacroiliitis. These inflammatory joint processes affect males more than females and do not parallel bowel inflammation. Ankylosing spondylitis classically presents with a stooped posture and worsening back pain/stiffness in the morning or at night and is improved with physical activity. Physical exam may reveal limited spinal flexion and X-ray imaging of the lumbar spine will show a “bamboo spine” that represents complete fusion of the bones (Figure 1A). Nearly all patients with IBD who have the genetic mutation in HLA-B27 will develop ankylosing spondylitis. IBD-associated sacroiliitis (Figure 1B) is most often bilateral in nature and can be either symptomatic or asymptomatic. Asymptomatic sacroiliitis can be seen in up to 50% of patients with CD.⁵ Spinal and axial disease are treated similarly to other spondyloarthropathies. Patients should be given a formal exercise plan and work closely with physical therapy to prevent deformities. Therapeutic agents that may also be used in axial arthritis include sulfasalazine, immunomodulators (methotrexate and azathioprine), and anti-tumor necrosis factor (TNF) therapy.

DERMATOLOGIC

Cutaneous EIMs may occur in up to 15% of patients with IBD and require dermatologic evaluation to confirm and assist in management.¹³ The two most common skin findings in IBD are erythema nodosum (EN) and pyoderma gangrenosum (PG). EN often appears on the extensor surfaces of the lower extremities, commonly the anterior tibial area, and is characterized by red raised tender nodules about 1–5 cm in diameter (Figure 2A). Although lesions may not be easily visible, physical exam will reveal tender palpable areas. Diagnosis is based on clinical judgement and skin biopsies are not necessary to make a diagnosis but would reveal inflammation of subcutaneous fat (panniculitis). EN shows a preponderance in females to males, associated with eye and joint involvement, and has a higher prevalence in CD than UC.¹⁴ The development of lesions parallels disease activity and thus treatment is aimed at addressing the ongoing bowel inflammation. Importantly, EN has been shown in a retrospective study to carry a 6-fold risk of development IBD within 3 years of presentation so this physical exam finding should prompt clinicians to always have a high index of suspicion for IBD.¹⁵ PG can be a debilitating skin disorder that occurs in about 5% of patients with IBD and is characterized by a discrete ulcer with a necrotic base, irregular violaceous edges, and purulent material which is sterile on culture. PG usually occurs on the lower extremities (Figure 2B) but may occur anywhere on the body notably, adjacent to a postsurgical stoma on the abdominal wall.¹⁶ These ulcers can range in size from a few centimeters to an entire limb. PG exhibits pathergy, a significant physiologic response to minor trauma or injury. Therefore, biopsy of the lesion should be avoided and the diagnosis is made clinically. It affects women more than men and it is unclear if PG has an association with clinical intestinal disease activity but in some instances may resolve with treatment of IBD. Mild cases may be treated with topical or local therapy that consists of steroid injections and moist dressings, but often

Figure 2. (A) Erythema Nodosum on lower extremities of a patient with IBD. (B) Pyoderma Gangrenosum. (C) Bowel associated dermatosis-arthritis syndrome (BADAS).

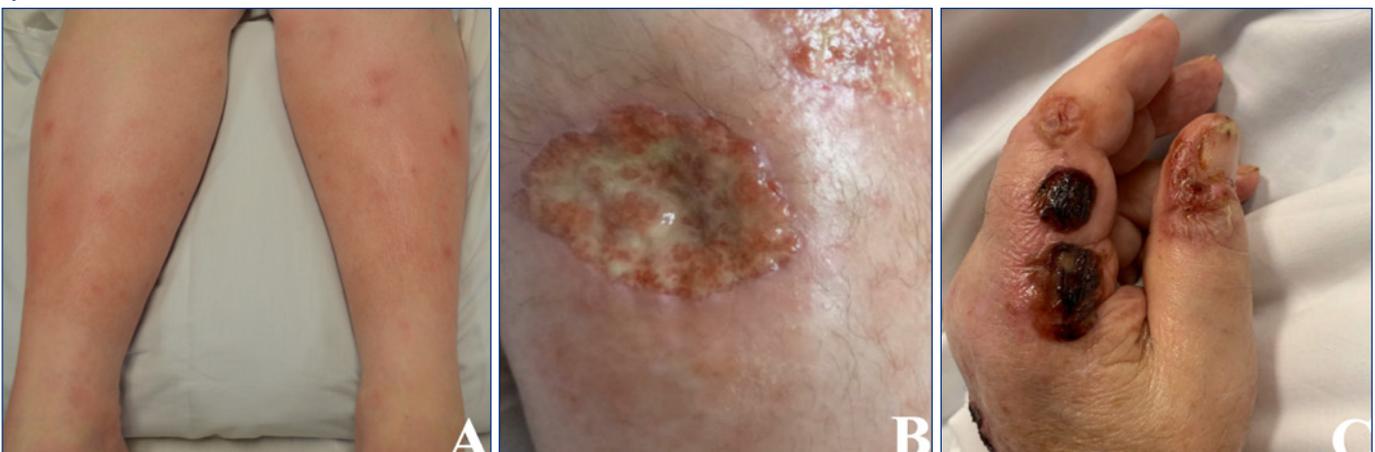
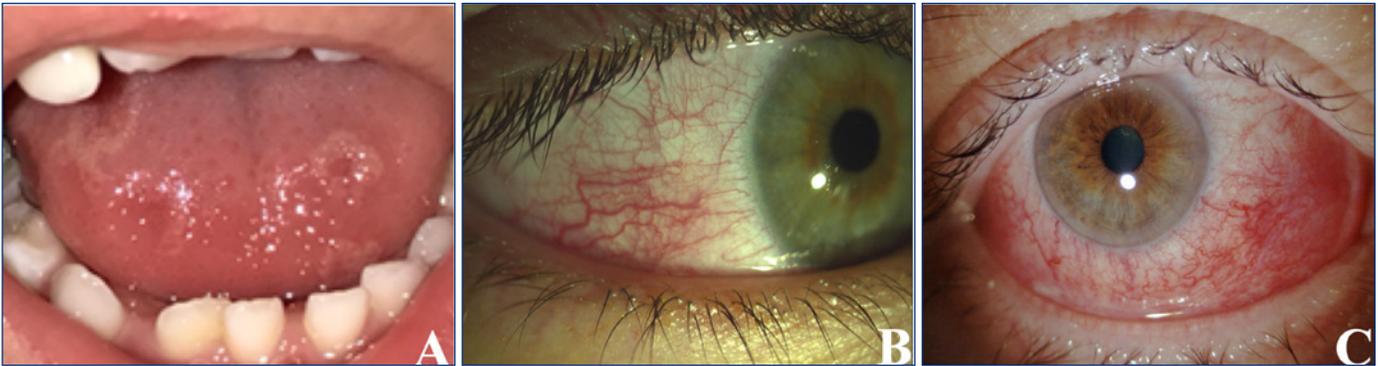


Figure 3. (A) Aphthous Stomatitis. (B) Episcleritis. (C) Scleritis.



systemic agents are needed that include dapsone, corticosteroids, and anti-tumor necrosis factor (TNF) therapy as well as involvement of a vascular surgeon specialist.

Acute febrile neutrophilic dermatosis, Sweet’s syndrome, is a rare EIM characterized by sudden onset tender erythematous papules and plaques on the upper extremities, trunk and face in association with fever and leukocytosis. Most cases occur in females, parallel intestinal disease activity, and are associated with other EIMs like arthritis. Treatment recommendations include topical or systemic steroids as well as adequate treatment of the IBD. Bowel associated dermatosis-arthritis syndrome (BADAS) is another rare neutrophilic dermatosis manifestation that was initially described in patients who had undergone ileojejunum bowel surgery but can also occur in patients with IBD. It presents with constitutional symptoms that include fever, arthritis, and arthralgias that precede an inflammatory skin eruption. Skin findings are characterized by erythematous macules that evolve into purpuric papules and vesiculopustular lesions on the upper extremities and trunk (Figure 2C). The pathophysiology is thought to involve immune complex creation in response to antigens from intestinal bacterial overgrowth that then deposit in the skin and synovium.^{17,18} Therapy for BADAS syndrome should focus on addressing the underlying intestinal inflammation in patients with IBD.

ORAL AND OCULAR

Oral lesions are common in patients with IBD but are found more often in patients with CD rather than UC, more prevalent in children compared to adults, and are found more commonly in men than women.¹⁹ The classic oral lesion associated with IBD is aphthous stomatitis, commonly referred to as a “canker sore”, presents as a shallow painful ulceration with a central fibrinous exudate and an erythematous boarder and can lead to symptoms of dysphagia or odynophagia. The lesions are commonly located along the buccal and labial folds but may also be present on the tongue (Figure 3A) or in the oropharynx. In a small number of patients, this may be the initial clinical exam finding

on presentation , but most often are diagnosed after intestinal involvement has occurred.²⁰ Aphthous stomatitis is common in the general population as well as other immune mediated diseases, but this finding is reported in up to 25% patients CD and 10% with UC.²¹ The presence of aphthous stomatitis becomes more severe with active bowel disease. Treatment mainly consists of topical steroids and anesthetics as well as addressing bowel disease with anti-inflammatory medications.

Pyostomatitis vegetans (PV) is a much less common occurrence but is an important oral manifestation of IBD for providers to be aware of. PV is commonly associated with UC but may also present in patients with CD. Intestinal manifestations will often predate PV development and patients will present with numerous tender miliary sterile pustular eruptions anywhere on the oral mucosa in a linear arrangement that may resemble “snail tracks.” Similarly, treatment of this presentation is achieved by addressing the bowel inflammation as well as topical steroids and antiseptic mouthwashes.

Ocular manifestations in IBD occur in 0.3–5%⁹ of patients and often associated with concomitant musculoskeletal manifestations. The ocular findings in patients with IBD that practitioners may encounter include episcleritis, scleritis, and uveitis. Being able to differentiate amongst these is of vital importance to early identify, appropriately treat, and prevent long-term patient morbidity (Table 3). Episcleritis is defined by hyperemia of the episcleral, which is the vascular plexus and fibrous tissue layer between the conjunctiva and sclera. It is a relatively benign manifestation and has no effect on vision. Eye exam reveals sectoral or diffuse patches of redness secondary to the inflamed superficial episcleral vessels (Figure 3B). Episcleritis often parallels bowel disease activity. Scleritis is a more pressing inflammation that affects the deeper layers of the eye, “the white of the eye”, and if not identified early can lead to visual impairment. Patients often have significant pain, classically deep boring pain that awakens the patient from sleep.²² One key exam feature to differentiate episcleritis from scleritis is the deep episcleral vascular plexus does not blanch when topical phenylephrine

Table 3. Clinical Differences Between Episcleritis, Scleritis, Uveitis

	Symptoms	Urgency Level	Diagnosis/Treatment
Episcleritis	Redness, burning, itching (Never any vision changes, photophobia, or change in pupillary response to light)	Non-Urgent	Redness within white patches of sclera. Blood vessels blanch when phenylephrine drops applied <ul style="list-style-type: none"> • Treat underlying IBD • Cool compress and/or topical steroids
Scleritis	Redness, eye pain with associated tenderness to palpation, deep boring pain that awakens patient from sleep	Urgent	No blanching of blood vessels when phenylephrine drops applied Violaceous hue <ul style="list-style-type: none"> • Systemic steroids or immunosuppression
Uveitis	Redness, eye pain, blurred vision, photophobia	Urgent	Requires slit lamp exam <ul style="list-style-type: none"> • Topical and systemic steroids • Severe/refractory cases may require systemic immunosuppression

is applied. In scleritis, the sclera may have a bluish hue that is representative of thinning of the sclera (**Figure 3C**). Uveitis is inflammation of the middle chamber of the eye (iris, ciliary body, and choroid) and occurs independently of bowel disease activity, but often in association with other EIMs. Patients will often present with ocular pain, headache, and blurred vision. Urgent ophthalmic exam via slit-lamp reveals the presence of perilimbal edema and inflammatory flare in the anterior chamber.²² Once identified, prompt initiation of topical and systemic steroids is vital and patients may require systemic immunosuppression with anti-tumor necrosis factor (TNF) therapy.

HEPATOPANCREATOBILIARY

Up to 50% of patients with IBD will experience hepatopancreatobiliary manifestations and complications during their disease course that may include gallstones, portal vein thrombosis, autoimmune hepatitis, autoimmune pancreatitis (Type 2), and primary sclerosing cholangitis (PSC). PSC is a chronic cholestatic liver disease that is characterized by fibrosis of the intrahepatic and extrahepatic bile ducts. Workup for PSC should be pursued in patients with IBD in the setting of elevated alkaline phosphatase or gamma-glutamyl transferase serum levels. Radiographic images will demonstrate multifocal bile duct strictures and segmental dilation, classically described as “beads on a string.” PSC is strongly linked to UC where at least 75% of patients with PSC have coexisting UC.⁹ Overall, a small number of patients with IBD will have PSC, 5% of UC patients and 2% of patients with CD (mainly colonic). Risk factors for the development of PSC in patients with UC are pancolitis, history of appendectomy, and male gender.²³ There is a strong association (10-fold risk) for the development of colorectal dysplasia/and or cancer in patients with PSC and therefore patients should undergo initial colonoscopy at the time of diagnosis and then yearly thereafter. Gallbladder polyps in association with PSC have a high malignant potential and therefore screening by yearly ultrasound and if found should

undergo treatment with cholecystectomy. Other potential complications that may arise from PSC include the development of acute bouts of acute cholangitis, cholangiocarcinoma, progression to liver fibrosis/cirrhosis, and acute decompensation requiring liver transplant.^{24,25} There are currently no recommended treatments for PSC and addressing the underlying bowel inflammation does not affect progression of PSC; however, management of patients requires a multidisciplinary team approach.

RENAL

Nephrolithiasis is prevalent at a higher rate in patients with IBD compared to the general population and represents an extraintestinal complication of IBD.²⁶ Renal stone formation can ultimately lead to repeated episodes of abdominal pain, chronic interstitial nephritis and, consequently, chronic kidney disease. One particular type of stone formation is closely associated with CD and an intact colon. Calcium-oxalate stones form due to depletion of bile acid salts secondary to inflamed or resected ileum. Bile acid salts are required for fat absorption; however, when inadequate amounts are present, fat can no longer be absorbed. This leads to calcium preferentially binding to fat rather than oxalate. Oxalate is then able to be easily reabsorbed by the colon and ends up in the urinary tract, leading to stone formation.

HEMATOLOGIC

Patients with IBD are at an increased risk for venous thromboembolism (VTE) such as deep vein thrombosis, portal vein thrombosis, and pulmonary embolus. The etiology is multifactorial in nature stemming from active inflammation, nutritional deficiencies, and hospitalizations/surgeries that lead to immobility. The risk for VTE in patients with IBD is 3-fold higher than the general population.²⁷ Several IBD-phenotype risk factors have been reported to be independent risk factors for VTE that include fistulizing disease, colonic involvement in CD, and extensive disease in patients with

UC.²⁸ The highest risk factor for VTE is in patients who are hospitalized with acute severe colitis.²⁹ Prevention of VTE is critical in IBD patients who are hospitalized and providers should order the appropriate prophylactic medications even in most settings of patient-reported gastrointestinal bleeding in order to prevent this complication.

CONCLUSION

EIMs are common in both CD and UC and may have profound impacts on patients. While some EIMs may parallel bowel disease activity, others have an independent disease course that requires lifelong management and monitoring. It is important for providers in all specialties to have an awareness of the prevalence and clinical presentations of EIMs to best identify and implement therapeutic treatments to improve the quality of life for patients with IBD.

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