**Reviewer’s Comments**

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**Inflammatory bowel disease:clinical features and manifestations beyond the bowel**

**Abstract.** Inflammatory boweldisease (IBD) encompasses a spectrum of diseases, with Crohn’s disease(CD) and ulcerative colitis(UC) representing thet wobroadestsub types of IBD. Multiple extraintestinal manifestations (EIMs) are more frequent in (IBD); 5% –50% of the patients might be affected. The most often implicated sites of manifestations are musculoskeletal and dermatological structures. However,while some symptoms like peripheral arthritis and erythema nodosum correlate with IBD progression, others have their own course of disease like axial arthropathy, gangrenosis of the pioderma and primary sclerosic cholangitis. This review would provide a summary of the most frequent EIMs and their prevalence.

**Key words**: Ulcerative colitis, Crohn’s disease, Inflammatory bowel disease

**1. Introduction**

Inflammatory bowel disease (IBD) is a chronic disease which relapses immune-mediated. The two major IBD subtypes are ulcerative colitis and Crohn's disease 1.Ulcerative colitis is a chronic, idiopathic inflammatory condition that affects the colon, most frequently affecting adults between 30 and 40 years of age with disabilities 2, 3 **.**It is characterized by relapse and remittance of inflammation in mucosal tissues, starting in the rectum and spreading to proximal colon segments. UC marked by cycles of recovery and cycles of recurrent, the latter, frequently presenting with a combination of abdominal pain vomiting, rectal bleeding, weight loss and malaise, is responsible for the vast majority of the disease burden and reduced quality of life 4, 5.

The risk for UC newly diagnosed patients is between 10% and 35% for five years and ultimately the long-term risk of colorectal cancer is enhanced by extensive and persistent inflammatory activity 6. The control of symptoms such as increased frequency of bowel movement and rectal hemorrhage was a controlled problem5. The introduction of standardized clinical scores, such as the Truelove and Witts criteria7 and the Mayo score5, allowed for a more accurate evaluation of the disease and, while they are sometimes used in clinical trials8, 9, have not yet been validated. This strategy, aimed at regulating and alleviating the effects of inflammation, did not target the inflammatory activity itself.

In comparison, there is a major correlation between clinical IBD and other disorders, such as irritable bowel syndrome (IBS) or infectious diarrhea 10, And some authors recorded a long-term recovery of UC patients with IBS-like symptoms (abdominal pain, elevated stool frequency) two to three times more frequency than controls 14. In contrast, others observed high stool frequency in up to 27% of patients with full endoscopic and histological healing, indicating a potential explanation for non-inflammatory functional intestinal damage 15. Finally, in a systematic study of clinical trials, clinical recovery during the placebo reached up to 15% 16. However, there is growing evidence that clinical improvement without mucosal healing (MH) is not associated with reduced hospitalization or colectomy rates over the years 17, 18.Inflammatory markers such as erythrocyte sedimentation rate, fecal marker calprotectin and serum markers C-reactive protein are other desirable choices for tracking UC patients11.

 Further studies are required to explain adequate surveillance strategies and cut-off rates before it is widely used in clinical practice.Mucosal inflammation is a central component of both UC and CD but, unlike Crohn's disease, a transmural disease with both strict and penetrating phenotypes, the development of the disease is limited to the UC mucosa 12. Therefore, it is no surprise that MH will prove an appealing target when addressing UC patients regardless of the severity of the disorder, inflammatory biomarkers or clinical presentation. Extensive research has been published over the past decade supporting the value of histological healing13, 14as it has shown excellent correlation with reduced risk of relapse15and hospitalization 16. In some studies, histological healing may be involved in the definition of MH in addition to the endoscopic findings 16.

The therapy is aimed at inducing and sustaining clinical and endoscopic remission.Current treatment choice for UC includes aminosalicylates, such as corticosteroids (including systemic corticosteroids such as hydrocortisone or prednisolone, and topical corticosteroids such as budesonide), mesalamine (5-aminosalicylic acid; 5-ASA) in both oral and rectal formulations, sulfasalazine,thiopurines (6-mercaptopurine and azathioprine), calcineurin inhibitors (tacrolimus and cyclosporine), anti-tumor necrosis factor (TNF)-a drugs (including infliximab, adalimumab, and golimumab), methotrexate andmore recently, the anti-integrin drug vedolizumab16.This review summarizesthe most common EIMs and itsclinical features and their prevalence and suggested management

**2. Extraintestinal manifestations**

UC and CD also cause extraintestinal manifestations (Table. 1), as seen in 25 to 40 % of patients with IBD 45. Almost every organ may be affected, but the primary manifestations are symptoms affecting the skin, eyes, joints and liver. Having one extraintestinal manifestation raises the likelihood that another will develop 46.

The treatment of underlying gut inflammation leads to the symptoms of concurrent disease activity such as erythema nodosum, episcleritis peripheral and arthritis. IBD can be associated with a specific disease, for example, IBD is closely correlated with primary sclerosing cholangitis (PSC); 75% of PSC patients have UC and 5 %to 10 % have CD. Nevertheless, only 5% of UC patients and 2% of CD patients develop PSC, respectively. 47. IBD patients are suffering from persistent diarrhea, usually with mucous and blood. For UC, symptom period may vary and appear to be more indolent, lasting weeks to months 17-19.

Extraintestinal manifestations in 21% -47% of patients with IBD are reported.1. Most extraintestinal manifestations are not well known for pathogenesis. In recent years, however, significant advances in the genetic basis of IBD have occurred with the advent of genomewide interaction studies. In particular, 99 susceptibility loci or genes have been reported to date (47 in ulcerative colitis and 71 in Crohn's disease)20.

Many organs may be involved withextraintestinal manifestations in IBD patients. Extraintestinal symptoms injoints,skin, hair have been correlated with the level of bowel inflammation, but cardiothoracic and gastrointestinal (hepatobiliary) desorption generally did nothave that correlation. 1.

**2.1 IBD Manifestations of gastrointestinal**

Pancreatic and hepatobiliary damageconsider the most severe extraintestinal manifestationsin IBD patients. While the relations between many liver disorders and IBD are well known, other associations are far more.21.

**2.1.1 Primary Sclerosing Cholangitis**

In the IBD setting, PSC is the most common hepatobiliary manifestation 20. PSC symptoms are progressive inflammation in the biliary tree, obliterative fibrosis and death, resulting in biliary fibrosis, cirrhosis and probable hepatic failure22. The PSC-IBD relationship was first identified by Smith and Loe in 196523.

**Table 1**. **Extraintestinal Manifestations of IBD**

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| --- | --- |
| **Gastrointestinal**  | Primary sclerosing cholangitis (PSC)PSC–autoimmune “hepatitis overlap syndrome”Drug-induced hepatitis Hepatic steatosisHepatic abscessPortal vein thrombosisPancreatitisImmunoglobulin G4 (IgG4)–associatedcholangitisPrimary biliary cirrhosisCholelithiasisAutoimmune pancreatitis |
| **Urinary** | Enterourinary fistulasObstructive uropathyNephrolithiasis |
| **Musculoskeletal** | Arthritis: ankylosing spondylitis, isolated joint involvementHypertrophic osteoarthropathy: clubbing, periostitisOther: aseptic necrosis, polymyositis |
| **Pulmonary** | Large airways diseasePneumonia |
| **Cardiac** | Congestive heart failure |
| **Ocular system** | Uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinalvascular diseaseConjunctivitisOrbital pseudotumor |
| **Dermatologic/Oral****system** |  Reactive lesions: erythema nodosum, pyoderma gangrenosum,aphthous ulcers, necrotizing vasculitis Specific lesions: fissures, fistulas, oral Crohn disease, drug rashes Nutritional deficiencies: acrodermatitis enteropathica, purpura,glossitis, hair loss, brittle nails Associated diseases: vitiligo, psoriasis, amyloidosis |
| **Hematologic** | Anemia, hyperhomocysteinemia |
| **Metabolic system** | Growth retardation in children and adolescents, delayed sexual maturation, osteopenia/osteoporosis |

**2.1.2 PSC**–**Autoimmune (Hepatitis Overlap Syndrome)**

In IBD patients, especially in ulcerative colitis patients, an association between autoimmune hepatitis and PSC has been reported. Several case reports of IBD patients who were initially diagnosed with autoimmune hepatitis later established PSC histological evidence 24.

**2.1.3 Cholangiocarcinoma**

The emergence ofcholangiocarcinoma, a crippling malignancy with an exceedingly poor prognosis, is a feared complication of PSC. Though cholangiocarcinoma does not result directly from IBD, the literature has well established a significantrelation between cholangiocarcinoma and PSC 1.PSC patients tend to show cholangiocarcinoma earlier than intermittent cholangiocarcinoma25.With a lifetime incidence of 5%-15%, PSC patients have a substantially higher chance of cholangiocarcinoma progress26.

**2.1.4 Drug-induced Hepatitis**

Although hepatobiliary disorders described above share common IBD pathogenesis; many medicines used to treat IBD can cause liver toxicity. A variety of medications have been involved, includingsulfasalazine,cyclosporine, thiopurines,methotrexate as well as certolizumab,adalimumab and infliximabas the biologic agents. Influenza-like symptoms andincreased liver enzymesin hepatotoxicity conditionusually resolve after the drug treatment has been discontinued 27 .

**2.1.5 Hepatic Steatosis**

The most hepatobiliary complication of IBD is hepatic steatosis, or fatty liver28. Agroup of researchers reported that 35% of the 511 IBD patients had a fatty liver disorder29. In published studies, fatty liver disease has been shown a massive variability in its prevalence (13% to 100%) 1. The level of fatty liver infiltration and the severity of colitis were found to be associated with ulcerative colitis patients.30. In IBD patients, the protein deficiency, corticosteroid therapy and chronic malnutrition, may lead fatty liver condition whilethe exact causesare somewhat unclear, 1.

**2.1.6 Hepatic Abscess**

The frequency of pyogenic liver abscesses in patients with IBD is slightly greater than in the general population28. Researchers indicated that the loss of barrier integrity of the intestine mucosamay lead toliver damage by an infectious agent through mesenteric veins1. In addition, portal vein associated- thrombosis can also occur in the portal pyelophlebitis condition31.

**2.1.7 Portal vein thrombosis**

In IBD patients, a thrombosis disorder is commonly observed at the portal vein 28.The levels of platelets, fibrinogen and factor V and VIII have been increased in patients with IBD, with antithrombin III being lowered, both of which may raise the risk of thrombosis. The IBD patients who have just undergone abdominal surgeryare more likely to develop portal vein thrombosis32. In patients with ulcerative colitis following restorative proctocolectomy, the portal vein thrombosis with a high incidence has been recorded 33.

**2.1.8 IBD and Pancreatic manifestations**

Concerning IBD-associatedpancreatic manifestationsin autopsies, in 1950, Ball et al. 34receded on pancreatic features accompanied by UC detected for the first time. In 1956, Chapin et al. 35described that histological changes in the pancreas with regional enteritis were mainly interlobar and periductal fibrosis and swelling of the acinar cells36.Subsequently, in US and Europe, researches on IBD, especially pancreatitis associated CD, have been recorded progressively since the 1970s37-39.

Pancreatic disorders related with IBD involve, pancreatic cancer (PC) acute pancreatitis (AP), chronic pancreatitis (CP), increasing of pancreatic enzymesandexocrine pancreatic insufficiency (EPI40.More details about pancreatic manifestations accompanied by IBDis shown inFig. 1.



**Figure 1**. Pancreatic manifestations accompanied by IBD.

**2.1.9 Other diseases associated with IBD**

**IgG4-associated cholangitis.** It was identified in individuals with diseases associated with IgG4with autoimmune pancreatitis, a relation between ulcerative colitis and cholangitis associated with IgG4 has beenobserved41.

**Primary biliary cirrhosis.** It is a characteristic autoimmune disorder of the hepatic tissue that arises through the progressive degradation of the inflammatory bile ducts and the obliteration of plasma cells and lymphocytes toward the portal way. The literature indicates a correlation between IBD and primary biliary cirrhosis but has not yet been widely recognized 42.

**Cholelithiasis.** Gallstones are commonly found in IBD patients. IBD progression and its pathophysiological changes may lead to gallstone development. A substantial correlation has been identified between cholelithiasis abnormality and Crohn's disease, with 13% and 34% as a prevalence rate43. The link between ulcerative colitis and cholelithiasis is uncertain, because, in ulcerative colitis patients,there does not seem to be a substantially elevated incidence of gallstones relative to the general population29.

**Autoimmune Pancreatitis**.A correlation between autoimmune pancreatitisand IBD have proposed by some researchers, while to date, the preciseassociation is not well-defined. It has been shown that IBD-associated pancreatitis has similar clinical, morphological, and histological characteristics to the same detected featuresin autoimmune pancreatitis43.

**3. Urinary manifestations of IBD**

In the IBD setting, the majority ofdifferent urinary complications have been reported in patients with Crohn's disease, with an incidence rate of 4% -23%.The complications are clearly appearing in people with serious or chronic illness. Urinary conditions can be directly or indirectly associated with the development of the disease44.

**3.1 Enterourinary Fistulas**

These disorders are the most comfortable urinary form inpatientswithIBD, a colo­vesical fistulas are the famous type of fistula. While,in Crohn's disease,gastrointestinal tract-confined fistulas are relatively common, fistulas between the urinary system and the gastrointestinal tract are much less common and severe complications, with an incidence rate of 2%-3.5% 44. Most patients with a well-known history of IBD are in their 4th or 5th decade. The incidence rate is high in males, due to the position of the adnexa and uterus in women between the intestines and the bladder45.

**3.2 Obstructive Uropathy**

Calculus obstructive uropathy is occurring in 1.9% – 6% of Crohn disease patients, is oftenignored urologic compli­cation of Crohn disease 44. Transmural bowel in­flammation may lead to hydroure­teronephrosis which followed by ureteral compression, fibrosis, or encasement and the right collecting ductsusually involved. 46.

**3.3 Nephrolithiasis**

IBD patients are 10–100 times more susceptiblethan other patients inthe hospital to develop nephrolithiasis, with 12 % as an incidence rate in patients withCrohn's disease 44. Adults with Crohn's disease are at higher risk relative to patients with ulcerative colitis than children47.

**4. IBD and musculoskeletal manifestations**

There are multiple musculoskeletal forms of IBD;almost 53% of patients have musculoskeletal system-related pain48.The most common sites involved in IBD arthropathy are axial and peripheral49.

**4.1 IBD-related Spondyloarthropathy**

This disease involves psoriatic arthritis, idiopathic ankylosing spondylitis, undifferentiated spondyloarthropathyand reactive arthritis. Spondyloarthropathy associated with IBD is divided into peripheral and axial arthropathy. Symptoms of axial type include back pain, sacroiliitis that triggers inflammation and spondylitis, whereas peripheral arthritis includes self-limiting nondeforming arthritis which develops and decreases with intestinal flares 50.

**4.2 IBD and arthropathy manifestations**

Arthropathy is common among IBD patients, and this condition is known as spondylarthritis (SpA).The SpA is further graded, based on the primary signs, as axial and peripheral51. A diagnosis of axial SpA is made using sacroiliitis radiographic findings consistent with symptoms of low back inflammatory pain. Radiological findings of sacroiliitis are significant in about 15%-27% of IBD patients,52-54while, progressive ankylosing spondylitis (AS) with syndesmophytes occurs in only about 3%-10% of patients.In addition, in Crohn's disease (CD) and AS patients, HLA‐B27 is found in approximately 25%–75% of cases, whereas in those with isolated sacroiliitis, HLA‐B27 is found in only 7%–15% of cases. HLA‐B27 Positivity in IBD patients suggests that these patients are at a higher risk of developing AS;55however, since HLA‐B27 positivity in idiopathic AS patients is significantly lower, it cannot be regarded as a diagnostic marker 52, 56.

**5. IBD and pulmonarymanifestations**

Black et al.57, in their analysis of population research, found that patients with IBD have pulmonary symptoms more often than the general population. Raj et al.58observed a four-fold rise in the incidence of IBD in their patients with airway disease in a 10-year retrospective study. The prevalence of disease-related pulmonary symptoms is highly variable and the symptoms continuum is broad. The pathogenesis of pulmonary findings associated with IBD is uncertain, but may be associated with an embryological origin of the intestinal mucosa and respiratory, a reaction with intestinal epithelium and lung antigen exposure, and/or an intestinal inflammatory mediator 59.

**6. IBD and cardiac manifestations**

To date, the link between cardiovascular disorders and IBD has not been completely explained. Researchers have indicated that patients with IBD have a higher risk of stroke,myocardial infarctionand cardiovascular mortality in recent years, particularly during the active stageof the disease. 60. The findings of Danish nationwide cohort studyrecorded high incidence of heart failure in patients with IBD that was highly associated with active bowel disease periods61. Other studies have proposed, however, that there is no correlation between increased cardiovascular disease incidence andIBD. Furthermore, a meta-analysis of 11 trials showed no increase in mortality ofcardiovascular patients between the control group the and IBD group 62.

**7. IBD and ocular systemmanifestations**

According to the findings ofthe population studyin the IBD setting,researchers have reported that the prevalence of ocular extraintestinal symptoms is between 4 % and 12 %63. The most common eye findings include inflammatory disorders affecting various areas of the globe, ranging from episcle­ritisandconjunctivitis to more serious conditions such as anterior uveitis and scleritis 64. Vision may be permanently compromised with scleritis, or anterior uveitis, while it is possible to detect unusual orbital extraintestinal manifestations of IBD with images59.

**8. IBD Skin diseases manifestations**

**8.1 Erythema nodosum (**EN**)**

EN is distinguished by the appearance of subcutaneous nodules raised, tender, purple, or violet (1–5 cm in diameter), which makes it simple to diagnose. 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. Also, EN is associated with other systemic symptoms such as arthralgia and fatigue. This can be clinically treated by removing the metastatic CD, and usually no biopsy is performed.

EN is the most common dermatological manifestation in patients with IBD and is more frequent in women and CD patients (4%-15% CD vs. 3%-10% CD cases).65, 66.EN is associated with IBD activity and flares in general but not with its severity67.Because of its connection with disease operation, management of the underlying IBD is the cornerstone of therapy. However, treatment with systemic corticosteroids may be needed in extreme cases, while treatment with infliximab, azathioprine or adalimumab may be required in resistant cases or those with repeated relapses68, 69.

**8.2Pyoderma gangrenosum**

PG is characterized by the formation of a skin pustule that quickly becomes a violent-edged burrowing ulcer, around 2–20 cm in diameter. PG occurs most often on the shins and adjacent to the stomas, though it can occur anywhere on the body, including genitals.It initially occurs as a single or multiple erythematous papule(s)/pustule(s), but subsequent dermis necrosis contributes to the production of deep excavating chronic ulcerations.

For PG, the histopathological findings are non-specific, and hence their diagnosis is made dependent on the characteristic findings of the lesions after excluding other possible skin diseasesbased on the typical findings of the lesions. In some cases, a biopsy from the periphery of the lesion may be required to exclude specific skindiseases. Therefore, a high index of suspicion is requiredto avoid misdiagnosis of PG55.

**CONCLUSIONS**

EIMs are moderately common through the IBD course not only limited to the gut,and in some cases, these EIM can be much more crippling than intestinal disease, which can occur long before IBD is diagnosed. Careful screening for EIMs in these patients and early appropriate diagnosis are imperative to reduce the overall morbidity. Increasing evidence suggests that IBD and associated ex­traintestinal disorders are not isolated diseases but share common mechanistic and pathophysiologic pathways, many of which remain elusive to date. In numerous cases, controlling the IBDactivity can also help in limiting the EIM; however, the further controlled trials remain the keys to development of the early differentiated diagnosis approach and promising treatment policies.

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**Conflicts of Interest**

The authors declare that they have no conflict of interest.

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