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REVIEW ARTICLE

INFLAMMATORY BOWEL DISEASE: CLINICAL FEATURES AND MANIFESTATIONS BEYOND THE BOWEL

Maged Almezgagi[1,2,7], Yu Zhang[2], Fadhl Al-shaebi[3], Mueataz A. Mahyoub[4], ALariqi Reem[5], Muhammad Shoaib[1], Emad Shamsan[2], Mohammed Gamah[1,2], Kamal Hezam[6], Abdul Baset Abbas[7], Wang Xiaozhou[1], Shen Xiangqun[1], Ma Qianqian[1], Ying Han[1], Ruhan Jia[1], Wei Zhang[1,2]△

[1]The Key Laboratory of high-altitude medical application of Qinghai Province, Qinghai Xining 810001, China.
[2]Department of Immunology, of Qinghai University, Qinghai Xining 810001, China.
[3]Department of Immunology, Hebei Medical University, Shijiazhuang, Hebei 050017, China.
[4]Department of Gastroenterology, Second Affiliated Hospital, Medical College of Xi'an Jiaotong University, Xi'an710004
[5]Department of Microbiology,Harbin Medical University,Harbin 150081,China.
[6]Nankai University School of Medicine, Tianjin 300071, PR China.
[7]Department of Medical Microbiology, Faculty of Sciences, Ibb University, Ibb City 70270, Yemen.

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***Address for Correspondence:**
Wei Zhang, The Key Laboratory of high-altitude medical application of Qinghai Province, Qinghai Xining 810001. Department of Immunology, of Qinghai University, Qinghai Xining 810001, China.
E-mail: *zw0228@qhu.edu.cn*

Abstract

Inflammatory bowel disease (IBD) encompasses a spectrum of diseases, with Crohn's disease (CD) and ulcerative colitis (UC) representing the two broadest subtypes 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.
Keywords: Crohn's disease, inflammatory bowel disease, Ulcerative colitis.

INTRODUCTION

IBD is a chronic disease which relapses immune-mediated. The two main IBD subtypes are UC and CD[1]. UC is an idiopathic, chronic condition in 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, beginning in the rectum then spreading to proximal colon segments. UC marked by cycles of recovery and cycles of recurrent, the latter, frequently presenting with the abdominal pain, vomiting, rectal bleeding, weight loss and malaise, is responsible for the most common of the disease problem[4,5]. The risk for UC newly diagnosed patients is between 10% and 35% for five years and ultimately the long-time risk of colorectal cancer is enhanced by extensive and persistent inflammatory condition[6]. The control of symptoms such as increasing in the bowel movement and rectal hemorrhage was a controlled problem[5]. The introduction of standardized clinical scores, such as the Truelove and Witts criteria[7] and the Mayo score[5], allowed for a more accurate evaluation of the disease and, while they are sometimes used in clinical trials[8,9], 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 patients[11]. 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 feature of both CD and UC but, unlike CD, a 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 healing[13,14] as it has shown great correlation with decreased risk of relapse [15]and hospitalization[16]. In some studies, histological healing may be involved in the description of MH beside the findings of endoscopy[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 rectal and oral preparations, sulfasalazine, thiopurines (6-mercaptopurine and azathioprine), calcineurin inhibitors (tacrolimus and cyclosporine), anti-tumor necrosis factor (TNF)-a drugs (including golimumab, adalimumab and infliximab), methotrexate and more newly, the anti-integrin drug vedolizumab[16]. This review summarizes the most common EIMs and its clinical features and their prevalence and suggested management.

Table 1: **Extraintestinal manifestations of IBD.**

Gastrointestinal	Primary sclerosing cholangitis (PSC), PSC–autoimmune "hepatitis overlap syndrome", Drug-induced hepatitis, Hepatic steatosis, Hepatic abscess, Portal vein thrombosis Pancreatitis, Immunoglobulin G4 (IgG4)–associated cholangitis, Primary biliary cirrhosis, Cholelithiasis, Autoimmune pancreatitis
Urinary	Enterourinary fistulas, Obstructive uropathy, Nephrolithiasis
Musculoskeletal	Arthritis: isolated joint involvement, ankylosing spondylitis, Hypertrophic osteoarthropathy: periostitis, clubbing Other: aseptic polymyositis, necrosis
Pulmonary Cardiac	Large airways disease, Pneumonia Congestive heart failure
Ocular system	Episcleritis, uveitis/iritis, scleromalacia, retinalvascular disease, corneal ulcers, Conjunctivitis, Orbital pseudotumor
Dermatologic/Oral system	Reactive lesions:pyoderma gangrenosum, erythema nodosum, necrotizing vasculitis, aphthous ulcers; Specific lesions: fistulas, fissures, drug rashes, oral Crohn disease; Nutritional deficiencies: purpura, acrodermatitis, enteropathica, hair loss, glossitis, brittle nails; Associated diseases: amyloidosis, psoriasis, vitiligo
Hematologic	Anemia, hyperhomocysteinemia
Metabolic system	Delayed sexual maturation, growth retardation in children and adolescents, osteoporosis/osteopenia

2. Extraintestinal manifestations

CD and UC also lead to extraintestinal manifestations (Table. 1), as shown in 25 to 40% of IBD patients[45]. Almost any part in the body at risk, but the primary manifestations are symptoms affecting the joints, liver, skin and eyes. Existing one extraintestinal symptoms 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 correlated with primary sclerosing cholangitis (PSC); 5% to 10% have CD and 75% of PSC patients have UC. Nevertheless, only 2% of CD patients develop PSC and about 5% of UC patients, respectively[47]. IBD patients who have 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 CD)[20]. Many organs may be involved with extraintestinal manifestations in IBD patients. Extraintestinal symptoms in joints, skin, hair have been correlated with the level of bowel inflammation, but cardiothoracic and gastrointestinal (hepatobiliary) desorption generally did not have that correlation[1].

2.1 IBD Manifestations of gastrointestinal

Pancreatic and hepatobiliary damage consider the most severe extraintestinal manifestations in 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 failure[22]. The PSC-IBD relationship was first identified by Smith and Loe in 1965[23].

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].

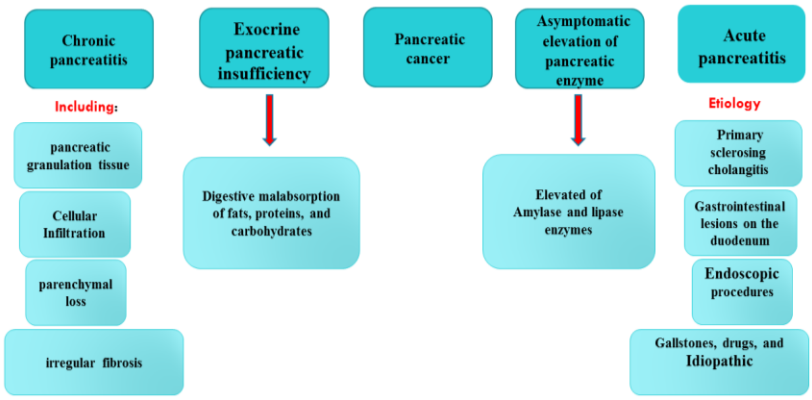

Figure 1: Pancreatic manifestations accompanied by IBD.

2.1.3 Cholangiocarcinoma

The emergence of cholangiocarcinoma, a crippling malignancy with an exceedingly poor prognosis, is a feared complication of PSC. Though cholangio-carcinoma does not result directly from IBD, the literature has well established a significant relation between cholangiocarcinoma and PSC[1]. PSC patients tend to show cholangiocarcinoma earlier than intermittent cholangiocarcinoma[25]. With a lifetime incidence of 5-15%, PSC patients have a substantially higher chance of cholangiocarcinoma progress[26].

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, including sulfasalazine, cyclosporine, thiopurines, methotrexate as well as certolizumab, adalimumab and infliximab as the biologic agents. Influenza-like symptoms and increased liver enzymes in hepatotoxicity condition usually 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 liver[28]. A group of researchers reported that 35% of the 511 IBD patients had a fatty liver disorder[29]. 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 while the exact causes are 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 population[28]. Researchers indicated that the loss of barrier integrity of the intestine mucosa may lead to liver damage by an infectious agent through mesenteric veins[1]. In addition, portal vein associated- thrombosis can also occur in the portal pyelophlebitis condition[31].

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 surgery are more likely to develop portal vein thrombosis[32]. In patients with ulcerative colitis following restorative proctocolec-tomy, the portal vein thrombosis with a high incidence has been recorded[33].

2.1.8 IBD and Pancreatic manifestations

Concerning IBD-associated pancreatic manifestations in autopsies, in 1950, Ball *et al.*,[34] receded on pancreatic features accompanied by UC detected for the first time. In 1956, Chapin *et al.*,[35] described that histological changes in the pancreas with regional enteritis were mainly interlobar and periductal fibrosis and swelling of the acinar cells[36]. Subsequently, in US and Europe, researches on IBD, especially pancreatitis associated CD, have been recorded progressively since

the 1970s[37-39]. Pancreatic disorders related with IBD involve, pancreatic cancer (PC) acute pancreatitis (AP), chronic pancreatitis (CP), increasing of pancreatic enzymes and exocrine pancreatic insufficiency (EPI). Pancreatic manifestations accompanied by IBD has been previously described by Iida *et al.*,[40] and summarized in Figure 1.

2.1.9 Other diseases associated with IBD

IgG4-associated cholangitis- It was identified in individuals with diseases associated with IgG4 with autoimmune pancreatitis, a relation between ulcerative colitis and cholangitis associated with IgG4 has been observed[41].

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 CD, with 13% and 34% as a prevalence rate[43]. The link between UC 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 population[29].

Autoimmune Pancreatitis- A correlation between autoimmune pancreatitis and IBD have proposed by some researchers, while to date, the precise association is not well-defined. It has been shown that IBD-associated pancreatitis has similar clinical, morphological, and histological characteristics to the same detected features in autoimmune pancreatitis[43].

3. Urinary manifestations of IBD

In the IBD setting, the majority of different urinary complications have been reported in patients with CD, 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 disease[44].

3.1 Enterourinary Fistulas

These disorders are the most comfortable urinary form in patients with IBD, a colovesical fistulas are the famous type of fistula. While, in CD, 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 bladder[45].

3.2 Obstructive Uropathy

Calculus obstructive uropathy is occurring in 1.9% – 6% of Crohn disease patients, is often ignored 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 ducts usually involved[46].

3.3 Nephrolithiasis

IBD patients are 10–100 times more susceptible than other patients in the hospital to develop nephrolithiasis, with 12% as an incidence rate in patients with CD[44]. Adults with CD are at higher risk relative to patients with ulcerative colitis than children[47].

4. IBD and musculoskeletal manifestations

There are multiple musculoskeletal forms of IBD; almost 53% of patients have musculoskeletal system-related pain[48]. The most common sites involved in IBD arthropathy are axial and peripheral[49].

4.1 IBD-related Spondyloarthropathy

This disease involves psoriatic arthritis, idiopathic ankylosing spondylitis (AS), undifferentiated spondy-loarthropathy and reactive arthritis. Spondylo-arthropathy 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 frequent among patients with IBD, and this condition is known as spondylarthritis (SpA). The SpA is classified based on the primary signs, as axial and peripheral[51]. A detection of axial SpA is achieved using sacroiliitis radiographic results consistent with signs of little back inflammatory pain. Radiological results of sacroiliitis are significant in around 15%-27% of patients with IBD[52-54], while, advanced AS with syndesmophytes develops in only nearby 3%-10% of patients. Moreover, in CD and AS patients, HLA-B27 is reported in approximately 25%–75% of patients, whereas, is recorded in about 7%–15% in those patients with sacroiliitis, HLA-B27. Positivity of HLA-B27 in IBD patients suggests that these individuals are more vulnerable to develop AS[55]; however, since HLA-B27 positivity in idiopathic AS cases is significantly lower, it cannot be regarded as a diagnostic indicator[52,56].

5. IBD and pulmonary manifestations

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.*,[58] observed 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 myocardial infarction, stroke and cardiovascular mortality in recent years, particularly during the active stage of the disease[60]. The findings of Danish

nationwide cohort study recorded high incidence of cardiac failure in individuals with IBD that was highly associated with active bowel disease periods[61]. Other studies have proposed, however, that there is no correlation between increased cardiovascular disease incidence and IBD. Furthermore, a meta-analysis of 11 trials showed no increase in mortality of cardiovascular patients between the control group and IBD group[62].

7. IBD and ocular system manifestations

According to the findings of the population study in the IBD setting, researchers have reported that the prevalence of ocular extraintestinal symptoms is between 4% and 12%[63]. The most frequent eye investigations include inflammatory disorders affecting various areas of the globe, ranging from episcleritis and conjunctivitis 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 by imaging tools[59].

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 outward of the limbs, mostly the frontal areas of tibial, are the most involved areas, and infrequently, the upper limbs or trunk may be involved. Also, EN is related with other symptoms such as weakness and arthralgia. This can be treated by removing the metastatic CD. EN is one the most observed dermatological manifestation in individuals with IBD and is high frequent in women and CD patients (4-15% CD vs. 3-10% CD cases)[65,66]. EN is linked with active IBD in general, however not by its severity[67]. Because of its connection with disease operation, management of the IBD is the cornerstone of therapy. Though, with systemically treatment by corticosteroids may be needed in extreme cases, while treatment with infliximab, azathioprine or adalimumab may be necessary in resistant situations or those with repeated relapses[68,69].

8.2 Pyoderma gangrenosum

PG is identified by the formation of a pustule on skin that quickly becomes a violent-edged burrowing ulcer, around 2–20 cm in diameter. PG occurs most often on the legs and close to the stomas, though it can happen anyplace over the body, including genitals. It initially occurs as a solitary or multiple red papule(s), but consequent dermis necrosis contributes to the production of deep gouge chronic ulcerations. For PG, the features of histopathological changes are non-specific, and hence their diagnosis is performed dependent on the characteristic findings of the lesions after ignoring other possible skin disorders depend on the distinctive results of the lesions. Occasionally, to confirm the diagnosis, a biopsy from the lesion may be needed[55].

CONCLUSIONS

EIMs are moderately common through the IBD course not only limited to the gut, and in some situations, these EIM can be much more crippling than bowel disease, which can occur long before IBD is diagnosed. Precise identifying for EIMs and early suitable analysis are imperative to reduce the overall morbidity. Substantial indication recommends that IBD and related extraintestinal illnesses are not isolated disorders but share common pathophysiologic pathways, to date, some of which remain indefinable. In numerous cases, controlling the IBD activity may aid 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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AUTHOR'S CONTRIBUTION

Almezgagi M: formal analysis, writing. **Zhang Yu:** editing, investigation. **Al-shaebi F:** methodology, investigation. **Mahyoub MA:** formal analysis, conceptualization. **Reem A:** review. **Shoaib M:** Study conception, design. **Shamsan E:** data acquisition. **Gamah M:** manuscript drafting, review. **Hezam K:** data curation, conceptualization. **Abbas AB:** critical revision. **Xiaozhou W:** writing, review, and editing. **Xiangqun S:** methodology, data curation. **Qianqian Ma:** writing, review, formal analysis. **Han Y:** writing, review. **Jia R:** methodology, investigation. **Zhang W:** formal analysis, conceptualization. All authors revised the article and approved the final version.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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