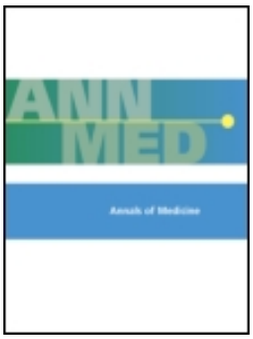

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REVIEW ARTICLE

Extraintestinal manifestations of inflammatory bowel disease: Epidemiology, diagnosis, and management

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Abstract

Extraintestinal manifestations occur rather frequently in inflammatory bowel disease (IBD), e.g. ulcerative colitis (UC) and Crohn's disease (CD). The present paper provides an overview of the epidemiology, clinical characteristics, diagnostic process, and management of rheumatic, metabolic, dermatologic (mucocutaneous), ophthalmologic, hepatobiliary, hematologic, thromboembolic, urinary tract, pulmonary, and pancreatic extraintestinal manifestations related to IBD.

Articles were identified through search of the PubMed and Embase databases, the Cochrane Library, and the web sites of the European Agency for the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA) (cut-off date October 2009). The search terms 'Crohn's disease', 'inflammatory bowel disease', or 'ulcerative colitis' were combined with the terms 'adalimumab', 'anemia', 'arthritis', 'bronchiectasis', 'bronchitis', 'cutaneous manifestations', 'erythema nodosum', 'extraintestinal manifestations', 'hyperhomocysteinemia', 'infliximab', 'iridocyclitis', 'lung disease', 'ocular manifestations', 'osteomalacia', 'pancreatitis', 'primary sclerosing cholangitis', 'renal stones', 'sulfasalazine', 'thromboembolism', and 'treatment'. The search was performed on English-language reviews, practical guidelines, letters, and editorials. Articles were selected based on their relevance, and additional papers were retrieved from their reference lists.

Since some of the diseases discussed are uncommon, valid evidence of treatment was difficult to obtain, and epidemiologic data on the rarer forms of extraintestinal manifestations are scarce. However, updates on the pathophysiology and treatment regimens are given for each of these disorders.

This paper offers a current review of original research papers and randomized clinical trials, if any, within the field and makes an attempt to point out practical guidelines for the diagnosis and treatment of various extraintestinal manifestations related to IBD.

Key words: *Crohn's disease, extraintestinal manifestations, inflammatory bowel disease, treatment, ulcerative colitis*

Introduction

Extraintestinal manifestations are relatively common in chronic inflammatory bowel disease (IBD) (1–4) and affect joints, skin, eyes, bile ducts, and various other organs (Table I). The most frequent rheumatologic manifestations are peripheral arthritis and axial arthropathies. Erythema nodosum and pyoderma gangrenosum are common dermatologic manifestations, whereas episcleritis, iridocyclitis, and uveitis are common ophthalmologic complications. Anemia is also seen frequently.

The rarer extraintestinal manifestations include bronchiectasis, bronchitis, and other lung diseases; hyperhomocysteinemia; osteomalacia; pancreatitis; primary sclerosing cholangitis; renal stones; and thromboembolism. All manifestations can be cumbersome for patients and physicians because the diagnostic process may be long and complex. The etiopathogenesis of most of the manifestations listed remains obscure, and the diagnoses in such cases are based solely on clinical and paraclinical manifestations. In the absence of an etiopathogenesis, treatment of the

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Key messages

- Extraintestinal manifestations are common in inflammatory bowel disease (IBD). The most prevailing extraintestinal manifestations are rheumatic (e.g. peripheral arthritis and axial arthropathies), dermatologic (e.g. erythema nodosum and pyoderma gangrenosum), ophthalmologic (e.g. episcleritis, iridocyclitis, and uveitis) and hematologic (e.g. anemia and hyperhomocysteinemia).
- Among the rarer manifestations are primary sclerosing cholangitis, pancreatitis, various lung disorders, osteoporosis, and thromboembolic events.
- All those manifestations are cumbersome for both patients and their physicians because the diagnostic process may be long and complex.

extraintestinal manifestations is often empirical, and the lack of randomized, controlled trials makes it difficult to obtain valid evidence of therapeutic efficacy. However, for many of the more frequent manifestations, newer biopharmaceuticals have been shown recently to be effective, e.g. in IBD-associated peripheral arthritis, pyoderma gangrenosum, and episcleritis.

The aim of the present review is to summarize the latest data on epidemiology, clinical features, and treatment of extraintestinal manifestations and to serve as a guideline for clinical use.

Table I. Extraintestinal manifestations of inflammatory bowel disease (IBD).

Rheumatic:	Peripheral arthritis
	Axial arthropathies
Metabolic:	Osteopenia/osteoporosis
	Osteomalacia
Dermatologic:	Erythema nodosum
	Pyoderma gangrenosum
	Aphthous stomatitis
	Sweet's syndrome
Ophthalmologic:	Uveitis
	Episcleritis
	Scleritis
Hepatobiliary:	Primary sclerosing cholangitis
	Cholelithiasis
Hematologic:	Anemia
Thromboembolic:	Hyperhomocysteinemia
Urinary tract:	Nephrourolithiasis
Pulmonary:	Chronic bronchitis
	Bronchiectasis
Pancreatic:	Pancreatitis

Review criteria

The search on 'Crohn's disease', 'inflammatory bowel disease', or 'ulcerative colitis' was combined with 'adalimumab', 'anemia', 'arthritis', 'bronchitis', 'cutaneous manifestations', 'erythema nodosum', 'extraintestinal manifestations', 'hyperhomocysteinemia', 'infliximab', 'iridocyclitis', 'lung disease', 'ocular manifestations', 'osteomalacia', 'pancreatitis', 'primary sclerosing cholangitis', 'renal stones', 'sulfasalazine', 'thromboembolism', and 'treatment' and was performed in the PubMed and Embase databases (cut-off date October 2009). English-language reviews, practical guidelines, letters, editorials, and articles were evaluated. Subsequently, articles were selected based on their clinical relevance, and additional papers were found in their reference lists. Other sources of information were the Cochrane Library and the web sites of the European Agency for the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA).

Rheumatic manifestations

Epidemiology

Inflammatory arthropathies are among the most common extraintestinal manifestations in IBD with a prevalence of 10%–35% and are found more commonly in patients with Crohn's disease (CD) (5,6). Asymptomatic sacroiliitis indeed may be seen in up to three-quarters of IBD patients. Careful questioning may also reveal many patients with a history of swollen joints and other musculoskeletal symptoms, often preceding the diagnosis of IBD by several years (7). The prevalence of axial arthritis varies from 3% to 25% of patients with IBD and may or may not be associated with peripheral arthropathy (7,8). In contrast to the male predominance in ankylosing spondylitis (AS), both sexes are equally represented among patients with IBD-associated spondyloarthropathy (SpA) (Figure 1). In some cases, joint manifestations may also become apparent years after colectomy in patients with ulcerative colitis (UC). It is uncertain, however, whether this can be ascribed to memory lymphocytes primed in a previously inflamed bowel or, rather, to development of a rheumatic disease *sui generis*.

Symptoms

Both axial and peripheral arthropathies with symptoms of arthralgia and swollen joints are viewed by many as reactive arthritides secondary to intestinal infections at least in some IBD patients. The list of possible etiologic agents includes intracellular bacteria (either obligatory or facultative aerobic) and invasive Gram-negative bacteria such as *Shigella*, *Salmonella*,

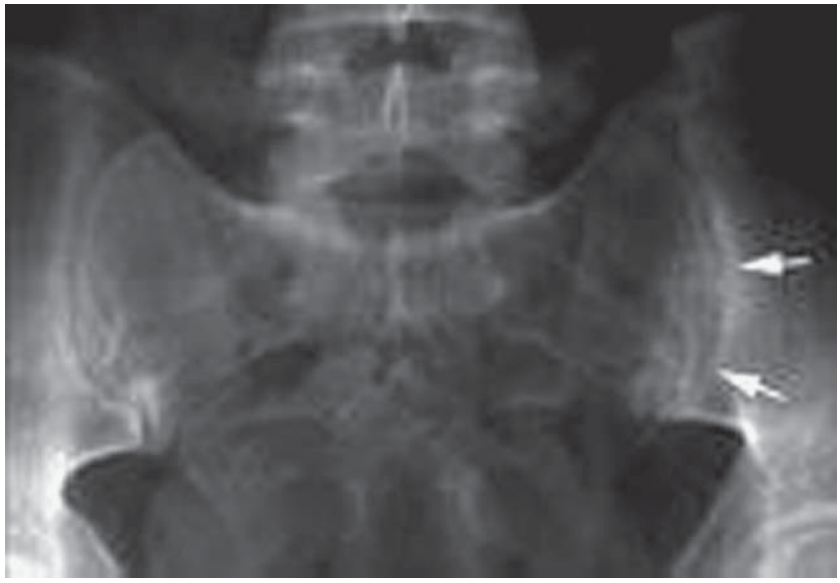

Figure 1. X-ray showing sacroiliitis.

Yersinia, and *Campylobacter* species. In most cases, however, there is no evident microbial culprit.

Axial involvement may vary from asymptomatic symmetric sacroiliitis to clinically evident inflammatory low back pain with decreased spinal mobility, extending to SpA fulfilling AS classification criteria and modifications thereof (9).

Diagnosis

The arthritides in IBD usually are divided into peripheral or axial arthropathies.

The peripheral arthropathies are characteristically seronegative, pauciarticular, asymmetric, migrating, and transitory, and they rarely result in joint destruction. However, joint manifestations often are associated with enthesopathy, tenosynovitis, and/or dactylitis, which may cause pain and compromise daily activities (10). Clubbing, periostitis, and granulomatous lesions of joints and bone have been described as well.

It is thought that reactive arthritis may arise as a result of T cell-mediated immune responses to bacterial antigens and degradation products circulating from gut to joint. Although there is no direct evidence to support the theory that viable bacteria colonize the joint, bacterial antigens, including lipopolysaccharides, have been detected in blood leukocytes and synovial fluid of patients with reactive arthritis and AS (11). Since T cells reactive to bacterial antigens have also been found in the joints of these patients, it is speculated that naive T cells may have been primed by bacterial antigens in inflamed gut mucosa in IBD and subsequently recirculate and home to joints, causing arthritis (7). This is supported by the often seen parallelism between flare-up of CD and peripheral arthritis. Other, albeit indirect, evidence for a bacterial role in CD-related peripheral arthritis comes from the fact that germ-free B27 transgenic rats develop colitis and arthritis only after restoration of the gut flora (12).

There are several genetic markers that may be involved, directly or indirectly, as components of extraintestinal joint and musculoskeletal manifestations in IBD. The human leukocyte antigen (HLA) system, for example, is considered one of the major genetic markers associated with many immunoinflammatory diseases, including IBD, and HLA-B27-positive IBD patients have a significantly higher risk of developing axial arthritis, including AS. In contrast, B27 is less often associated with peripheral arthropathy in IBD. Indeed, this complication seems to segregate into at least two phenotypes, each of which with immunogenetically distinct features (13). Thus, type 1 arthropathies are associated with HLA-DRB1*0103, B35, and B27, and type 2 arthropathies are associated with B44, suggesting that the two types of arthritic complications in IBD may have different etiopathogenesis. It has also been reported that UC patients with the HLA-DRB1*0103 phenotype have a higher risk of arthritis (8).

Altered bacterial handling and gut permeability may also be of pathogenic importance for the extraintestinal manifestations of IBD. For example, the CD-susceptibility gene *caspase activation and recruitment domain–containing protein 15* (*CARD15*)/*nucleotide-binding oligomerization domain 2* (*NOD2*) encodes an intracellular pattern recognition receptor with binding affinity for peptidoglycan, a component of muramyl dipeptide, which is an important

bacterial pathogen-associated component (14). Polymorphisms in *CARD15* are known risk factors in CD, and these genetic variants also appear to be strongly associated with IBD and the presence of SpA (15). Interestingly, the *CARD15* mutants associated with CD are loss-of-function mutants, i.e. they fail to activate the inflammatory pathway mediated by nuclear factor-kappa B (NFκB) (16). Thus the *CARD15* mutations governing IBD and its extraintestinal manifestations may function through a decreased production of antibacterial polypeptides that, in turn, alters the enteric flora and, consequently, gut permeability and mucosal inflammation.

A diagnosis of inflammatory lower back pain should include pain during the night and at rest that improves with movement, in addition to lack of radiologic abnormalities. A diagnosis of IBD-associated AS includes low back pain and morning stiffness for more than 3 months associated with a decreased mobility of the lumbar spine and limitation in chest expansion combined with radiologically evident sacroiliitis. HLA-B27 also is heavily associated with AS in cases linked to IBD.

Treatment

Treatment of peripheral arthritis in IBD primarily involves treatment of the underlying intestinal disease. This usually improves the joint symptoms, and further therapies are unnecessary in mild cases. If arthropathy persists seemingly independently of the bowel disease, therapies are similar to those of the primary articular diseases. Hence non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, may be used as in patients with rheumatoid arthritis (RA). Caution is advocated, however, because the gastrointestinal side-effects of NSAIDs may aggravate the underlying bowel disease, although the evidence is weak (7). Today there is insufficient evidence to warrant NSAID avoidance among those IBD patients who really need them for joint symptoms, and it is not yet clarified if COX-2 inhibitors are safer than classical NSAIDs in IBD (17). However, a careful follow-up of IBD patients, mainly those in remission, is recommended in the first weeks of treatment with NSAIDs. At present, further randomized, double-blinded trials are needed to address this issue further (18). Glucocorticoids, often part of the basic treatment regimen, are also highly effective on the arthritic manifestations. In patients with oligoarthritis, local injection of glucocorticoids is effective as well. Biologic response modifiers, particularly antibody constructs targeted against the cytokine tumor necrosis factor α (TNF-α), are effective in about two-thirds of RA patients and will also improve peripheral arthritis in most IBD patients who are responders to biologics.

Treatment of axial arthropathies in IBD is also focused on reducing the activity of the underlying bowel disease. Therapy is otherwise similar to that used in classic AS, i.e. to reduce the inflammatory activity and to prevent deformity. NSAIDs are effective in reducing inflammation and pain but may not affect progressive spine destruction and may aggravate the intestinal disease. While sulfasalazine has been shown in several studies to be effective in AS, its effect in IBD-associated SpA is less clear, and it may be effective only on peripheral joint involvement (5). While methotrexate may be effective in AS, concrete evidence for effect in IBD-associated AS is scarce (5). Anti-TNF-α drugs, particularly infliximab and adalimumab, are effective in most IBD patients with SpA, and these agents are often recommended if patients fail to respond adequately to NSAIDs (19). Physical therapies and exercise are as important in these patients as in other forms of SpA.

Metabolic manifestations

Osteopenia and osteoporosis

Epidemiology. IBD is associated with an increased risk of developing osteoporosis (20) (Figure 2). The prevalence rates range from 2% to 30% and, for osteopenia, from 40% to 50% (20–22). The T score is proposed by the World Health Organization (WHO) as the strongest determinant of fracture risk. *T score* is defined as the number of standard deviations (SDs) by which a given bone mineral density (BMD) measurement exceeds or falls below the normal mean BMD of healthy 30-year-old individuals (peak bone mass). A BMD that is up to 1 SD below peak bone mass is considered normal; at 1–2.4 SDs below peak, BMD is considered to indicate osteopenia and mild or moderate bone deficiency; at 2.5 SDs or more below peak, BMD is labeled osteoporotic with marked bone deficiency (20).

Symptoms. Osteoporosis might be without symptoms for decades until fractures suddenly occur. Some osteoporosis fractures, especially of the back, may even be without initial symptoms and are first diagnosed at a later stage when pain arises related to the location of the fractures. Hip fractures typically occur as a result of a trivial accident. Osteopenia is without symptoms, but as this condition progresses, the diagnosis changes to osteoporosis.

The role of glucocorticoids is complex. Some studies show an important relationship between dosage, duration, and pattern of glucocorticoid therapy, and these factors are related to the incidence of pathologic fractures (20,23). Other studies report that the IBD and not the use of glucocorticoids relates to the reduced BMD (24,25).

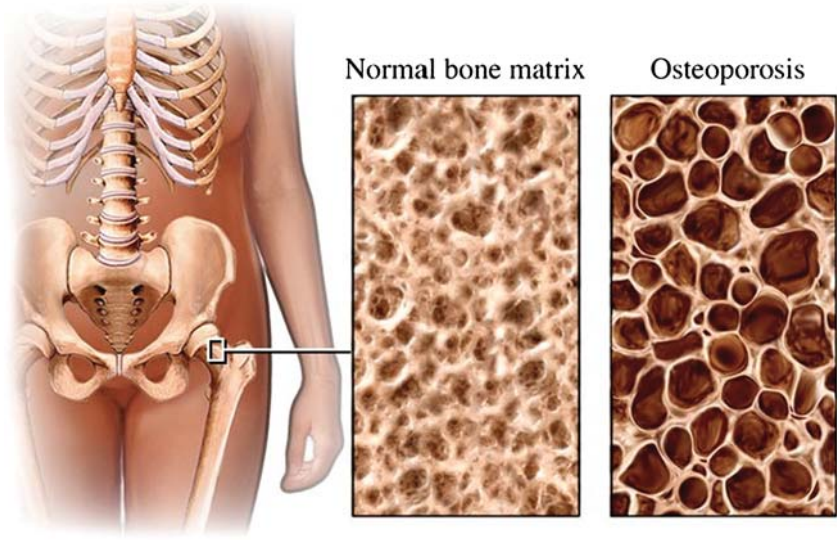

Figure 2. The decalcified osteoporotic bone.

Disease duration has not been established as a significant factor for low BMD because some studies report no effects, whereas others indicate a positive relationship between length of disease (i.e. duration) and a lower BMD (22,26–30). Furthermore, the disease activity has no effect on BMD according to findings from some studies, whereas other studies report that BMD is higher with an increasing duration of quiescent disease (22,26,31).

Diagnosis. Diagnosis is based on dual X-ray absorptiometry (DEXA) scanning and the T score.

Both the American College of Gastroenterology and the American Gastroenterological Association recommend selective screening of IBD patients with DEXA scans. The criteria include a postmenopausal state, on-going glucocorticoid treatment, cumulative prior use of glucocorticoids exceeding 3 months, history of low-trauma fractures, and an age greater than 60 years (20).

The pathogenesis is multifactorial, and the bone loss depends significantly on the age (above 60 years), gender, use of glucocorticoids, and grade of systemic inflammation (i.e. intestinal disease activity correlates with the risk of fracture) (8). Recent research has shown that interleukin 6 (IL-6) is a pathogenic factor that results from loss of estrogen and has implicated this cytokine in the physiopathology of several other diseases caused by an increased osteoclastic bone resorption, including diseases such as RA (20). Genetic variations in the IL-6 and IL-1 receptor antagonist genes identify IBD patients at risk for increased bone loss. Other genes, including *LRP5* and the vitamin D receptor (*VDR*) gene, are seen in association with increased risk of bone loss (20).

Treatment. It is well known that supplementation with calcium and vitamin D is essential for bone metabolism. Several studies have shown that calcium and/or vitamin D or its analogs have a small benefit in BMD as well as a small controversial age-dependent trend (though not totally clear) in the reduction of bone fractures, especially of the spine in postmenopausal women (20,32). All patients receiving glucocorticoid treatment should have supplements of calcium and vitamin D as daily prophylaxis.

Bisphosphonates, an antiresorptive analog of pyrophosphate, have proven effective in increasing BMD and reducing fractures of the spine, hip, and wrist in the treatment of osteoporosis in postmenopausal women (20,33–35). Estrogens increase the BMD in patients under glucocorticoid treatment, but the effect on prevention of bone fractures remains unclear. Estrogens are not recommended for this purpose, and they are known to increase the risk of breast cancer (20,36). Raloxifene is a selective estrogen receptor modulator that has been approved for the prevention and treatment of postmenopausal spinal osteoporosis. However, no studies with raloxifene have yet been performed in IBD patients. Teriparatide (a genetically engineered fragment of human parathyroid hormone) stimulates new bone formation, leading to increased BMD. No studies have been performed in IBD-associated osteoporosis (20). Some clinicians suggest that teriparatide should be considered for the treatment of patients with an established glucocorticoid-induced osteoporosis who require long-term steroid treatment (37).

Osteomalacia

Epidemiology. Osteomalacia is a rare complication in IBD (38,39), and the prevalence is 30%–40% among those with a small intestinal resection (40). It is characterized by a decreased bone matrix mineralization and is a common clinical finding associated with calcium and vitamin D deficiency. It may occur in IBD patients with significant small bowel resections in the absence of vitamin D supplementation. Patients with an altered bile salt resorption, such as those with involvement of the terminal ileum or ileal resections or those who receive bile acid-sequestering agents, are at greatest risk of developing vitamin D malabsorption (41).

Symptoms. Osteomalacia manifests as progressive, generalized bone pain, muscle weakness, hypocalcemia, and pseudofractures and in its late stages as a 'waddling gait' (42).

Diagnosis. Biochemical abnormalities include low serum calcium, phosphorus, and vitamin D concentrations, as well as elevated alkaline phosphatase and parathyroid hormone concentrations. Classic radiologic features include pseudofractures, biconcave vertebrae, and a triradiate pelvis (42).

Although osteoporosis and osteomalacia both result in low BMD, apart from elevated bone alkaline phosphatase levels, osteomalacia can be distinguished from osteoporosis only through a bone biopsy, but this is rarely pursued (38).

Treatment. For patients with vitamin D deficiency, vitamin D doses at 1000 units/day are sufficient (43). However, larger doses (4000–50,000 units/day) may be necessary in some patients with malabsorption (42). The goal in treating patients with vitamin D should be to maintain serum 25-hydroxy vitamin D (25-OHD) levels higher than 25 ng/mL (38).

Dermatologic (mucocutaneous) manifestations

Erythema nodosum

Epidemiology. Erythema nodosum (EN) (Figure 3) is the most common cutaneous manifestation associated with IBD (44,45). EN affects 2%–20% of the IBD population (2,46,47). Women are affected more commonly than men (44,48). EN is believed to be a delayed hypersensitivity reaction, the antigen being identified in approximately 40% of patients (44). However, in most patients, the manifestation is without apparent cause (idiopathic) (44).

Symptoms. The primary lesions are raised, deep-red, tender, warm, and round nodules, 1–5 cm in diameter, distributed symmetrically over the anterior lower legs. Occasionally, they also appear on the trunk, upper extremities, and face (44,49). Neither ulceration nor scarring occurs in EN. EN typically is associated with exacerbation of the IBD but not with the severity or extent (44,48).

Diagnosis. Biopsies that show focal panniculitis generally are not necessary because the diagnosis may be secured on the characteristic clinical appearance (45,49). The differential diagnosis of EN includes other types

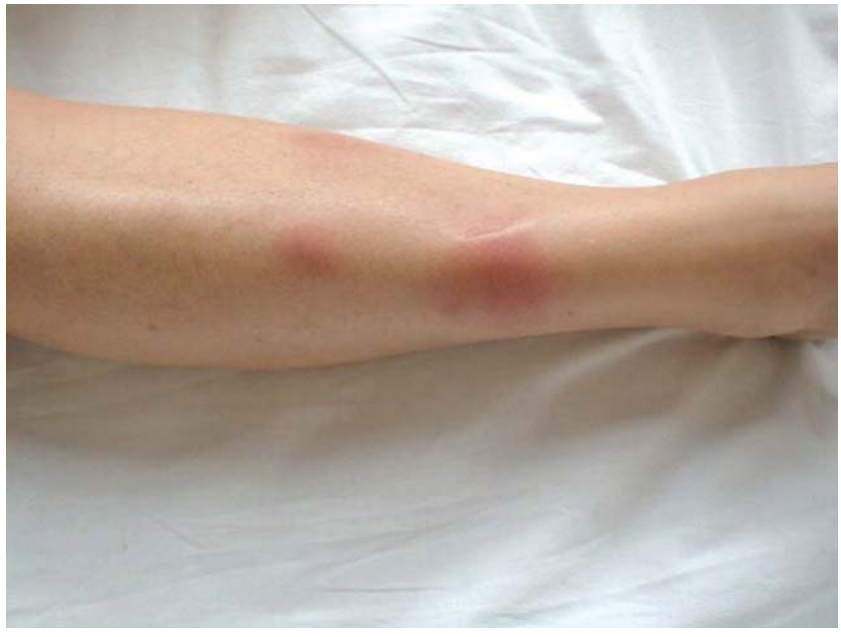

Figure 3. Erythema nodosum localized on the anterior crus.

of panniculitis, cutaneous infections, and subcutaneous lymphomas (44).

Treatment. The disease is self-limited with an excellent prognosis. The time to remission is, on average, 5 weeks. Supportive treatment with compression stockings, leg elevation, and rest may be sufficient. For severe cases, glucocorticoids may be applied (44). Dapsone and infliximab have been reported to be successful in treating severe or refractory lesions (49).

Pyoderma gangrenosum

Epidemiology. Together with Sweet's syndrome (see below), pyoderma gangrenosum (PG) belongs to a group of diseases called the *neutrophilic dermatoses*. These immune-mediated inflammatory conditions of the dermis are characterized by the unpredictable development of chronic ulcerated skin lesions, up to 70% of which are distributed to the lower extremities. Another common lesion site is peristomal; in fact, this is a pathergic phenomenon that occurs in about one-quarter of patients with PG (50).

PG affects 0.5%–2% of the IBD population (2,46, 50). Conversely, about one-third of patients with PG suffer from IBD (51).

Symptoms and diagnosis. PG is characterized by a painful deep ulcer with a violaceous undermined border and a necrotic purulent center. It typically affects the legs but may occur in any area of the skin, sometimes even as peristomal ulcers (44).

There are no absolute diagnostic tests for PG, and the disease has no absolute histologic appearance. The diagnosis ultimately is based on a combination of clinical and histologic features (50). The differential diagnosis of PG includes cutaneous infections, Sweet's syndrome (see below), cutaneous malignancies, vasculopathies, collagen-vascular diseases, and halogenodermas (44). A skin biopsy will confirm the clinical suspicion, and it helps to exclude other disorders that mimic PG. The histologic findings vary depending on the area biopsied as well as on the age of the lesion (44,50). Typical features include a diffuse inflammatory infiltrate within the dermis, evidence of surface ulceration, features of an acute folliculitis, and fibrinoid changes within blood vessels (50). Ulcerations appear in the later stages (44).

Treatment. There is a lack of randomized clinical trials concerning the treatment of PG, and the literature is largely founded on small case series and personal experience. The essence of the treatment of PG is cleansing and appropriate dressings for the ulcers and appropriate therapy for the underlying bowel disease. Local wound therapy should be guided by a wound care specialist and include stringent wound care, analgesia, and treatment of secondary infections. Local wound care consists of lavage with sterile saline, topical antibacterial creams, and hydrocolloid dressings. Oral prednisolone in doses up to 1 mg/kg (and no more than 40 mg/day) are usually effective in rapidly controlling PG (50,52,53). In mild cases, a combination of glucocorticoids and dapsone has been used successfully with an initial dosage of dapsone of 100 mg/day orally, gradually increasing to 200–300 mg/day (50,54). Steroid-dependent patients require immunosuppressive treatment with azathioprine/6-mercaptopurine, which has a delayed onset of efficacy of a minimum of 8–10 weeks. Anti-TNF-α treatment has been reported to be effective, and anti-TNF-α has become the drug of choice in steroid-refractory PG; initial doses of 5 mg/kg, with repeat treatments depending on response, have been recommended (50,52,55–57).

Aphthous stomatitis

Epidemiology. Aphthous stomatitis is the most common oral lesion in IBD (Figure 4). The incidence is 4%–20% (53). This manifestation, however, also appears in 15% of the background population. This complication generally occurs during active stages of the intestinal disease, and it responds favorably to treatment.

Recurrent aphthous ulcerations are more frequent in IBD patients with other extraintestinal manifestations (53).

Symptoms. Aphthous stomatitis consists of shallow round ulcers with a central fibrinous membrane and an erythematous halo (48).

Diagnosis. This manifestation is associated with IBD and cannot be differentiated clinically from common aphthous stomatitis (48). The differential diagnoses include oral herpes simplex, Behçet's disease (58), and coxsackievirus infection. Oral herpes simplex and coxsackievirus lesions begin as vesicles that later ulcerate. Aphthous stomatitis does not have a vesicular stage.

Treatment. Treatment of the underlying bowel disease is often curative. For symptomatic pain relief, 2% viscous lidocaine is frequently used. Treatment with topical corticosteroids such as triamcinolone 0.1% paste once to three times per day is effective in promoting healing. In addition, 5% amlexanox paste may be beneficial (48,59). Systemic glucocorticoids should be used only in refractory cases or in persistent or severe aphthous stomatitis (48).

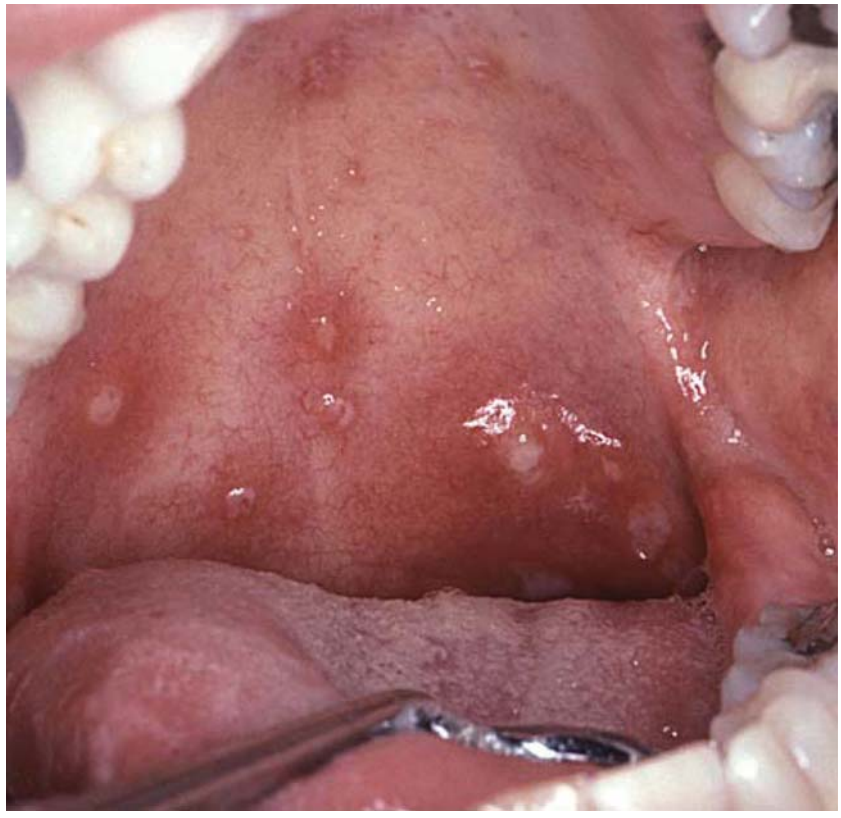

Figure 4. Aphthous stomatitis.

Sweet's syndrome

Epidemiology. Sweet's syndrome is a rare disease; only about 35 cases associated with IBD have been reported in the literature (60). It is also named *acute febrile neutrophilic dermatosis.* The syndrome predominantly affects women (61).

Symptoms and diagnosis. Sweet's syndrome is a cutaneous lesion characterized by a constellation of clinical symptoms including pyrexia, tender erythematous skin lesions (papules, nodules, and plaques), and a diffuse infiltrate consisting predominantly of mature neutrophils typically located in the upper dermis, often in the face, neck, and upper limbs. The histologic findings are characterized by a neutrophilic infiltrate with leukocytoclasis (62).

Treatment. Most cases respond to systemic treatment with glucocorticoids (63). Treatment with anti-TNF-α antibodies has also been successful (61,64).

Ophthalmologic manifestations

The incidence of ocular involvement in IBD varies from 2%–29% according to the published literature (65–67).

Uveitis

Epidemiology. Anterior uveitis (iridocyclitis) (Figure 5) occurs in up to 17% of the IBD population (65,67). The incidence of uveitis of the posterior segment in some studies is reported as rare (<1%); other studies report frequencies of up to 10% (65,66). Uveitis is often associated with coexisting joint and skin manifestations. This condition is characterized by inflammation of the vascular coat of the anterior eye, i.e. the iris and the ciliary body (iritis), and the posterior eye, i.e. the vitreous (vitritis), choroid, or retina (68).

Symptoms. Anterior uveitis often presents as a painful eye with visual blurring and photophobia. A seriously affected eye will be miotic and may have an abnormal papillary response to light (68).

Diagnosis. The eye redness associated with uveitis is unique in that it exhibits a 'ciliary flush' with redness most intense at the limbus and radiating outward for a short distance. Definitive diagnosis is made by slit-lamp examination (68).

Treatment. Topical glucocorticoids are the primary treatment for uveitis, and they successfully prevent blindness or corneal perforation (69). A number of studies describe anti-TNF-α antibodies (infliximab) as a successful treatment (5,47,69,70).

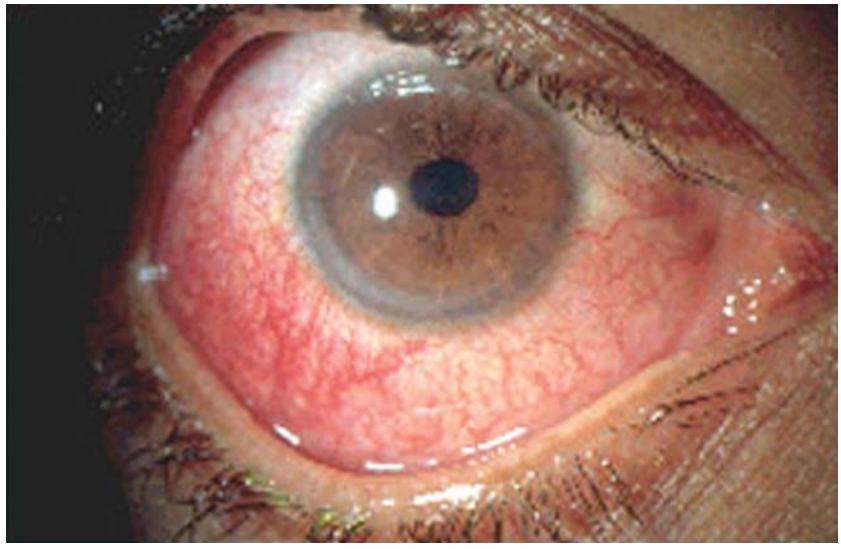

Figure 5. Red eye as a result of uveitis.

Episcleritis

Epidemiology. Episcleritis occurs in up to 29% of IBD patients. It may be diffuse or nodular and may be unilateral or bilateral (65,66).

Symptoms. Episcleritis is characterized by acute redness, hyperemic patches and complaints of irritation or burning. Pain or tenderness to palpation is common. Episcleritis is not associated with loss of vision, photophobia, or loss of a normal papillary response to light. Episcleritis is usually related to the activity of the underlying IBD. An ocular examination reveals focal or diffuse patches of redness within which white patches of sclera can be seen between the dilated episcleral vessels (68).

Diagnosis. For diagnosis, see the following section on scleritis.

Treatment. Application of cool compresses and/or topical glucocorticoids may be sufficient in conjunction with appropriate treatment of the underlying IBD (68,71).

Scleritis

Epidemiology. Scleritis occurs in up to 18% of all IBD patients (65).

Symptoms. Scleritis may impair the vision, and patients often complain of severe eye pain associated with tenderness to palpation. The deep scleral vessels are hyperemic along with the episcleral and conjunctival vessels. This may cause the inflamed area to appear violet when viewed in natural light (68).

Diagnosis. Scleritis can be distinguished from episcleritis in that the sclerae appear pink between the dilated surface vessels, whereas the sclerae are white in episcleritis (68).

Treatment. Recurrent scleritis may result in scleromalacia (66). Scleritis can lead to retinal detachment or optic nerve swelling. It therefore requires aggressive treatment with systemic glucocorticoids and/or immunosuppressants (68,71,72). Although evidence is still scarce, biologics such as the B lymphocyte-depleting drug rituximab may be beneficial in the treatment of inflammatory ocular diseases in IBD (73,74).

Hepatobiliary manifestations

Primary sclerosing cholangitis

Epidemiology. Primary sclerosing cholangitis (PSC) is a chronic immunoinflammatory disorder of the bile ducts with a multifactorial and polygenic etiology. Thus the preponderance of HLA-A1, -B8, -DR3, -DR6, and -DR2 in PSC, combined with the protectional haplotype -DR4, suggests that an inappropriate immune response may play a pathogenic role (75). There is a strong but incompletely understood association between PSC and IBD, and PSC is more frequent in UC than in CD. Thus a Swedish study has shown that 82% of all PSC patients also had IBD (76), whereas only 35% of southern Europeans (77) and only 20% of Japanese IBD patients have this association (78). On the other hand, between 3% and 7% of patients who have UC also have PSC (79). PSC is predominantly a disease of younger men, with a male:female ratio of 2:1.

A German study has shown that the estimated time from diagnosis to either death or orthotopic liver transplantation is 9.6 years, with 40% of all

PSC patients being transplanted (80). A Canadian study has shown that the annual incidence of PSC is 0.92 cases per 10^5 patient-years (81). Concurrent IBD does not affect the long-term prognosis of this complication. PSC may, however, be associated with other malignancies, including colorectal cancer (82). Hepatobiliary malignancy (especially cholangiocarcinoma) was observed in 14% of the population.

Symptoms. PSC may present with intermittent jaundice, fatigue, weight loss, right upper quadrant abdominal pain, and pruritus. Many patients are commonly asymptomatic, and the diagnosis is suspected by finding an abnormally elevated serum alkaline phosphatase concentration with otherwise normal liver function tests. Acute cholangitis does not occur commonly, except after instrumentation of the biliary tract system.

Diagnosis. Diagnosis is established by elevated serum levels of alkaline phosphatase, sometimes associated with elevated alanine transaminase, combined with cholangiographic abnormalities; i.e. strictures and beading of the bile ducts might be observed by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) (Figure 6). Although ERCP has a specificity and sensitivity close to 100%, significant complications are associated with this procedure, which has led to an increased use of MRCP as the diagnostic tool (83,84). Meagher and colleagues have analyzed potential decision models to reach the most cost-effective strategy to investigate suspected PSC patients. A strategy of an initial MRCP followed by ERCP, if required, was established in this context (84). If in doubt about the diagnosis, a liver biopsy will show inflammatory changes of a normal cholangiogram with pericholangitis (85).

Treatment. Ursodeoxycholic acid has not been demonstrated to improve either symptoms or mortality, although it has been demonstrated to improve liver biochemistry (86,87). However, the drug reduces the incidence of colonic dysplasia and carcinoma, including cholangiocarcinoma and colorectal cancer (88). Pruritus has been treated with cholestyramine, rifampicin, and naltrexone, but there are still no controlled trials regarding medical treatment of PSC. A double-blind, placebo-controlled, randomized study of infliximab in the treatment of PSC failed to show any benefit after six infusions (89). Orthotopic liver transplantation remains the only established treatment for PSC, and it has an 85%–90% 5-year survival (90). Disease recurrence in the allograft, however, is a recognized complication in approximately 20% of patients undergoing transplantation (91).

Prognosis. The onset of PSC may be unrelated to the onset of UC symptoms and activity. Although IBD symptoms usually precede the diagnosis of PSC, some patients develop PSC before IBD (92). Coexisting PSC increases significantly the cumulative risk of colorectal cancer (CRC), particularly in patients with UC (82). The median survival time for PSC patients from diagnosis is 12 years in symptomatic patients, but approximately 75% of asymptomatic patients survive for 15 years or more (77). The median

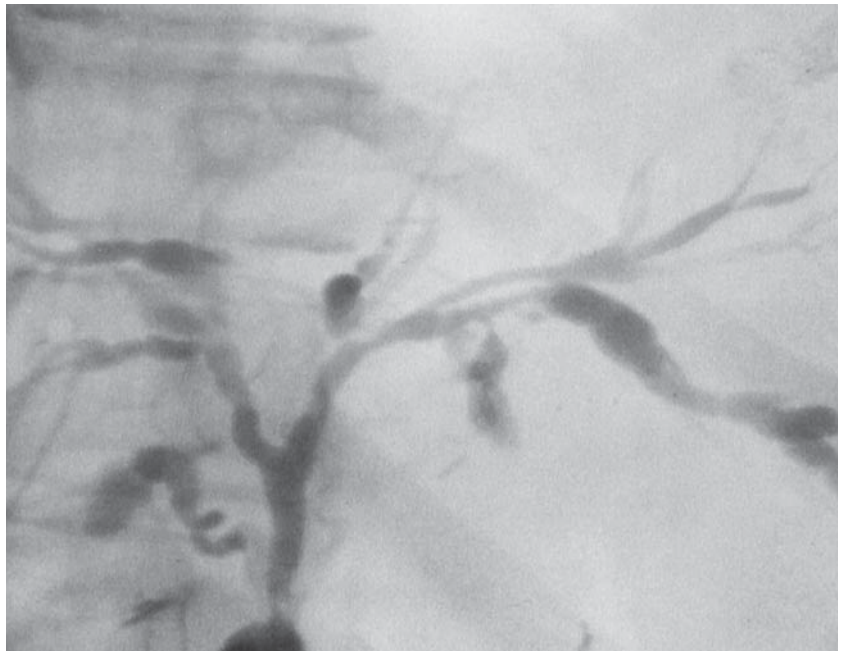

Figure 6. Primary sclerosing cholangitis visualized by endoscopic retrograde cholangiopancreatography (ERCP).

survival after diagnosis of cholangiocarcinoma is 9 months (93).

Cholelithiasis

Epidemiology. The relationship between IBD and gallstones has been recognized for more than four decades (94), in particular among patients with CD, with a prevalence ranging from 13% to 34% (95–98). However, many of these patients have been selected at referral centers owing to other complications, and the actual figure therefore may be lower, limiting the precision of the estimates. The risk of developing gallstones in patients with UC is unclear because the findings are limited or contradictory. Thus two studies have found the prevalence of gallstones to be higher among UC patients than in the general population (99,100). Two other studies showed the opposite results (96,101). An Italian study including 429 patients with CD and 205 patients with UC followed up to 11 years showed that only CD patients had a significantly higher risk of developing gallstones than did matched hospital controls. Site of disease at diagnosis, lifetime surgery, extent of ileal resections, number of clinical occurrences, total parenteral nutrition, and frequency and duration of hospitalizations were independently associated with gallstones (102).

The incidence rate of gallstones is approximately 14 per 1,000 patient-years in CD compared with 8 in matched controls (including UC) (102).

Symptoms. Symptoms are abdominal pain under the right curvature after meals in association with nausea and in some cases vomiting. A frequent finding is elevated blood levels of alkaline phosphatase.

Diagnosis. The diagnosis is established by ultrasound investigations.

Treatment. The treatment of gallstones are laparoscopic cholecystectomy or extracorporeal shock-wave lithotripsy (103).

Hematologic manifestations

Anemia

Epidemiology. The prevalence of anemia in patients with IBD ranges from 9% to 74% depending on the patient subpopulation (104). *Anemia* generally is defined as a hemoglobin value of less than 7 mmol/liter or a hematocrit value of less than 0.4, and *severe anemia* is defined as a hemoglobin level of less than 6 mmol/liter (104). Two predominant types of anemia have been identified in the context of IBD (105): iron-deficiency anemia and anemia of chronic disease.

Symptoms. The symptoms are often rather non-specific, including pale skin and mucous membranes, tiredness, and dizziness.

Diagnosis. Iron deficiency anemia is caused by chronic blood loss, chronic inflammation, malnutrition, hemolysis, and bone-marrow-suppressing medication. Iron deficiency anemia occurs because inflammation and ulceration, which are the prominent pathophysiologic manifestations of IBD, can result in chronic intestinal bleeding and loss of iron. Thus iron deficiency occurs only when iron loss exceeds absorption, usually owing to a blood loss over several weeks (106). In addition, chronic abdominal pain and nausea often result in poor oral intake, and mucosal inflammation in the gastric tract may further lead to inadequate nutrient absorption. Although iron absorption tends to be normal in patients with UC and CD, the iron loss may exceed the patients' capacity for iron absorption.

Anemia of chronic diseases is described as a non-specific consequence of activation of the inflammatory cytokine network, which results from an ineffective erythropoiesis and a shortened red blood cell survival (105,107). Patients may experience an up-regulated ferritin synthesis and a down-regulated transferrin synthesis, leading to dysfunctional iron transport to the bone-marrow. These mechanisms are mediated by cytokines such as TNF-α, interferon-γ, IL-1, and IL-6 (105). It is important to identify the nature and severity of anemia in IBD so that therapy can be targeted at the underlying mechanism(s).

Treatment. Oral iron supplementation or administration of intravenous iron might be helpful. In very severe cases, erythropoietin (EPO) should be administered (104,108). However, double-blinded, placebo-controlled trials are needed to validate whether EPO agents and intravenous iron supplementation significantly influence disease activity and quality of life (104).

Thromboembolic events

Epidemiology

An activation of the coagulation cascade and platelet aggregation during systemic inflammation are observed in IBD with an elevated risk of venous thromboembolic complications (109–112). In a population-based study, the incidence of deep vein thrombosis and pulmonary embolism among IBD patients was 30 and 10–20 per 10,000 patient-years, respectively (113). IBD patients have more than a 3-fold increased risk of developing venous thromboembolism (VTE) compared with the general population (113). Thus

thromboembolism represents a significant cause of morbidity and mortality. Most IBD patients with VTE have active disease (112). Corticosteroid treatment per se may cause a hypercoagulable state with an increased risk of thrombosis, but data pointing to a significant association are missing.

A recent American study investigated rates of VTE among hospitalized IBD patients over a 6-year period. A multivariate adjustment showed that patients with both UC (odds ratio (OR) 1.85) and CD (OR 1.48) had higher rates of VTE than did non-IBD patients (111). Active fistulizing disease in CD was independently associated with a greater risk of VTE (111). VTE was associated with a greater mortality among IBD patients (adjusted OR 2.50). The age and co-morbidity-adjusted excess mortality from VTE was 2.1-fold higher for IBD patients than for non-IBD patients (111). These findings underscore the need for more widespread prophylaxis and an early detection of VTE among IBD patients.

Prophylaxis

Unless in the presence of hemodynamically significant gastrointestinal bleeding, unfractionated or low-molecular-weight heparin injections should not be contraindicated for admitted IBD patients in neither the treatment nor the prophylaxis of VTE.

Hyperhomocysteinemia

Epidemiology. Hyperhomocysteinemia is more common in IBD patients than in control individuals, and this condition is associated with an increased risk of thromboembolism as well (114). The reported frequency of hyperhomocysteinemia in IBD varies from 11% to 52% (114), which is significantly higher than in the control population (3.3%–5%) (114). Lack of vitamin B_6, B_{12}, and folate or the use of folate-inhibiting drugs such as methotrexate and sulfasalazine may contribute to an acquired hyperhomocysteinemia (115–118).

Diagnosis. The diagnosis of hyperhomocysteinemia is made based on a fasting plasma level of more than 15 μmol/liter (119).

Treatment. Vitamins, especially folate, and vitamins B_6 and B_{12} are essential because the condition is fully reversible with this nutritional supplementation. Both European and American societies recommend a fasting homocysteine level of less than 10 μmol/liter as a therapeutic target (120).

The known link between hyperhomocysteinemia and VTE in IBD (121) warrants intervention studies to clarify a more optimal treatment of IBD in the future.

Urinary tract manifestations

Nephrourolithiasis

Epidemiology. The incidence of urinary calculi in IBD is 8%–19% in contrast to only 0.1% in the general population (122). The risk is higher in CD than in UC. Most patients with CD and stones in the urinary tract have had bowel surgery, with extensive bowel surgery yielding the highest risk (123).

Kidney stones in IBD are composed primarily of calcium oxalate or uric acid (urate) (123). Calcium oxalate stones are associated with ileal CD and related to an increased urinary oxalate excretion to some extent caused by an increased intestinal absorption. The increased intestinal oxalate absorption is caused by bile salt malabsorption in the diseased or resected distal ileum, which results in bile salt deficiency and fat malabsorption. Under normal conditions, most dietary oxalate is bound to calcium and is poorly absorbed. However, malabsorbed fats bind luminal calcium, minimizing the amount bound to oxalate and resulting in an increased oxalate absorption (123). Another potential course of calcium oxalate stones is lower urinary concentrations of stone inhibitors (i.e. citrate and magnesium) relative to the stone promoter (i.e. calcium) (124,125).

Urate stones are related to lengthy diarrhea or small bowel ostomies and form as a result of intestinal fluid and bicarbonate losses, which lead to a concentrated, acidic urine. This favors the precipitation of urate, even though IBD patients with urate stones do not necessarily have an elevated blood concentration or urinary excretion of uric acid (123).

Symptoms. Typical symptoms are intermittent colicky flank pain that may radiate to the lower abdomen or groin, often associated with nausea and vomiting (122,126).Once a stone enters the ureter, lower urinary tract symptoms such as dysuria, urgency, and frequency may occur. Physical examination often reveals flank or lower abdominal tenderness (126).

Diagnosis. Microscopic hematuria combined with the typical symptoms of renal colic is highly predictive of urolithiasis, but stones may occur in the absence of hematuria. An unenhanced helical computer tomography (CT) scan is the best radiographic test for diagnosing urolithiasis in patients with acute flank pain. If the symptoms are not caused by urolithiasis, a CT scan can often identify the actual cause. Most kidney stones are visible on CT scans (126).

Treatment. Patients with IBD and renal stones should be treated conservatively in the same way as patients without IBD (122). This includes rehydration (127), pain control, and alkalinization of the urine, e.g. with potassium citrate 30 mEq (base) per day, especially

in urate stone patients (122,123,128). Potassium-magnesium citrate (42 mEq potassium, 21 mEq magnesium, and 63 mEq citrate) also reduces the recurrence of calcium oxalate stones (129). Although these conservative treatments are effective in most cases, urologic therapy including endoscopic lithotripsy and/or percutaneous nephroureterolithotomy is necessary in some cases (122). If urate stones recur, allopurinol 300 mg/day might be indicated (123,130).

Prophylactic treatment of oxalate stones consists of a low-oxalate diet (avoidance of spinach, rhubarb, beets, nuts, tea, cola, chocolate, wheat bran, and strawberries) and supplementation with oral calcium 1–2 g/day (123). Administration of thiazide diuretics has been shown to reduce the recurrence of calcium oxalate stones (131,132).

Pulmonary manifestations

Chronic bronchitis and bronchiectasis

Epidemiology. Several pulmonary diseases have been reported in IBD, including bronchiectasis (133–135) and chronic bronchitis (136). The pulmonary diseases should be separated from interstitial lung diseases owing to sulfasalazine or mesalazine treatment, although this may be difficult in some cases.

Several studies have shown subclinical pulmonary abnormalities in 50%–60% of the IBD population (137–139). The most prevalent abnormality is a reduction in gas transfer (transfer coefficient for carbon monoxide DLCO) of about 50% (138) and an elevation of the residual volume:total lung capacity (RV:TLC) ratio (139).

An increased disease activity is associated with abnormal pulmonary function, suggesting a direct pathogenic link to IBD (139,140). Although the exact mechanism is unknown, reports have shown that there is a shift of the inflammatory process from the bowel to the lung, perhaps related to the common ancestry of the bowel and the bronchial tree (138,139). Additionally, the gut-associated lymphoid tissue shares adhesion molecules that are involved in the homing of leukocytes to both gut and bronchiolar lymphoid tissues (138,139).

Most pulmonary manifestations occur subclinically. The most frequent airway disease is bronchiectasis (133–135,141), and it is commonly associated with systemic diseases such as RA and systemic lupus (141). Bronchiectasis typically is associated with UC. The second most frequent airway disease is chronic bronchitis (136,141).

Symptoms. The symptoms of bronchiectasis as well as chronic bronchitis are cough and copious amounts of sputum production. Some IBD patients with diseases of the airway system may have a non-productive cough, and some may have functional dyspnea (141,142).

Diagnosis. Excessive sputum volume, purulence, and tenacity are non-specific findings in both bronchiectasis and chronic bronchitis. The physical examination findings in these patients may reveal stethoscopic abnormalities and clubbing, or they may be normal (142). Because bronchiectasis is defined as an abnormal dilation of the airways, the diagnosis depends on visualizing the typical changes either radiographically or anatomically. Bronchiectasis is sometimes obvious on routine chest radiographs, but the diagnosis is usually established using high-resolution CT (HRCT) scanning (142). The key feature of bronchiectasis on HRCT scans is an enlarged internal bronchial diameter, where the bronchi appear larger than the accompanying artery (the signet ring sign). Other HRCT scan findings in bronchiectasis include air-fluid levels in dilated airways and identification of airways in the extreme lung periphery (142).

Chronic bronchitis is defined as a disease of the bronchi that manifests with cough and sputum expectoration occurring on most days for at least 3 months of the year and for at least 2 consecutive years when other pulmonary or cardiac causes for the chronic productive cough have been excluded. Evaluation of these patients should include a complete history regarding exposures to respiratory irritants, including different kinds of smoke (143).

Treatment. There is a lack of clinical trials involving treatment of bronchiectasis. However, the American College of Chest Physicians recommend that treatment of bronchiectasis should consist of pharmacotherapy to enhance bronchodilation and to improve mucociliary clearance, antibiotics to prevent and treat recurrent infections, maneuvers designed to mobilize secretions (e.g. chest physiotherapy), mucolytic agents, and, occasionally, surgery to treat localized disease. Surgery to resect the bronchiectatic lung should be limited to patients with local disease who have not responded to medical therapy.

The goal of treatment generally is to improve the symptoms of cough, sputum production, and dyspnea and to prevent the progression of airway damage (142).

The treatment of chronic bronchitis consists of short-acting beta-agonists to control bronchospasm and to relieve dyspnea and ipratropium bromide to improve cough (143–145). Central cough suppressants such as codeine and dextromethorphan are recommended for short-term symptomatic relief of coughing (143).

Pancreatic manifestations

Pancreatitis

Epidemiology. IBD patients are at increased risk of developing both acute (146) and chronic pancreatitis (147), and a recent study also indicates that the less common autoimmune pancreatitis occurs more often among these patients (148). Pancreatitis may be caused most often by drugs used in IBD, especially 5-aminosalicylates (5-ASA) (116), azathioprine, and 6-mercaptopurine (149).

Non-IBD epidemiologic studies suggest an overall incidence of 0.1%–2% (149), but patients with IBD have an extremely higher risk factor owing to the drugs but also owing to gallstones and other potentially contributing factors, including pancreatic autoantibodies (150–152).

Symptoms. Severe abdominal pain in the epigastric region and nausea and vomiting are the predominant symptoms.

Diagnosis. Diagnosis of pancreatitis requires two of the following three features: 1) abdominal pain characteristic of acute pancreatitis, 2) serum amylase or lipase concentration three times or more above the upper limit of normal, or 3) characteristic findings of acute pancreatitis on a CT scan (124). Diagnosis of drug-induced pancreatitis is often difficult because there are no unique clinical, biochemical, or radiologic features to distinguish this etiology of pancreatitis from other causes of pancreatitis. The diagnosis of autoimmune pancreatitis also requires immunohistochemistry of biopsy specimens (148).

A careful evaluation should be performed to exclude other common causes. Important information from the history should include alcohol use, biliary tract disease or gallstones, a family history of pancreatitis, actual medication, abdominal surgery, abdominal trauma, and weight loss. Blood tests within the first 24 hours should include liver function tests and calcium and triglyceride determinations. An abdominal ultrasound should be obtained on admission to assess for gallstone symptoms. The most usual symptom is severe abdominal pain with or without nausea and vomiting.

Treatment. Suspected drugs must be discontinued to prevent any on-going pancreatic injury. Further management should include aggressive intravenous fluid replacement, frequent checking of vital signs (including monitoring of oxygen saturation), and relief of abdominal pain with parenterally administered narcotic medication (124). Patients with signs of organ dysfunction should be transferred to an intensive care unit for close observation and management. In more severe cases of pancreatitis, nutritional support may be needed, particularly when it becomes clear that the patient will not be able to eat for a week or more (124). If feasible, enteral nutrition should be given in preference to parenteral nutrition (124).

Drugs to suspect include azathioprine and 6-mercaptopurine (derived non-enzymatically from azathioprine), especially in CD patients. Severe side-effects of acute pancreatitis are seen in approximately 5% of all CD patients (153–155) and very rarely in patients treated with azathioprine for UC or other diseases (156). Azathioprine-induced pancreatitis is a very severe side-effect with no known pathogenic mechanism. Circulating pancreatic autoantibodies (PABs) are found in approximately 30% of patients with CD (150). PABs are not found in healthy individuals nor in patients with other gastrointestinal diseases (157). Since PABs and azathioprine/6-mercaptopurine-induced pancreatitis are both specific items for CD, the link between them was investigated recently in a Dutch study (157). However, it was not confirmed that all CD patients with azathioprine/6-mercaptopurine-induced pancreatitis were PAB-positive.

5-ASA may also cause acute pancreatitis, and this drug is used mostly among UC patients (116). The symptoms of acute pancreatitis from this drug or from azathioprine/6-mercaptopurine usually develop within the first 3 weeks of the first dose (116).

Prognosis. Acute pancreatitis is a severe disease with an overall mortality of 5% (even up to 30% in patients with necrotizing pancreatitis and infected necroses); it seems that the drug-induced pancreatitis observed in IBD has a much more benign nature, but epidemiologic studies in this subgroup are not available.

General conclusions

It is evident from the present review that IBD frequently involves various organs beyond the intestine. The management of IBD patients therefore requires the physician to pay attention to the symptoms of extraintestinal manifestations discussed herein. To minimize suffering of individual patients, physicians should also be aware of the latest treatment regimens, which, fortunately, accumulate at a high pace.

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