Extraintestinal Manifestations of Inflammatory Bowel Disease

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Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) have been reported to involve almost every organ system. This article focuses on the prevalence (where known) and clinical aspects of the more commonly described EIMs of Crohn disease (CD) and ulcerative colitis (UC). Because of limited data from pediatric populations, much of the information in this review is from adult reports. An important consideration is whether EIMs represent manifestations of the same pathogenetic mechanisms or distinctly different disease processes from the underlying IBD, possibly coincidental to the presence of IBD or as a consequence of the IBD or its treatment. EIMs may present before the onset of gastrointestinal symptoms, during the natural course of disease, and rarely may even follow colectomy in patients with UC.

The prevalence of at least 1 EIM in recent population-based studies of patients with IBD ranges from 6% to 47% (1–4). Several reports from pediatric centers suggest a greater prevalence in younger patients. Grossman and DeBenedetti (5) reported that 68% of 41 children with IBD had EIMs, and a recent review of pediatric patients by Stawarski et al (6) reported that 50% with UC and 80% with CD had at least 1 EIM.

In this review, we provide an overview of EIMs that have been reported to be associated with UC and CD, emphasizing the pediatric experience when such information is available. EIMs are subdivided into several categories: colitis related, specifically skin, eye, joint, and mouth, where the activity of the EIM parallels the activity of the underlying intestinal disease; hepatobiliary; impaired growth; EIMs secondary to complications of or as direct extensions of bowel disease, more frequently noted in patients with CD than with UC and including nephrolithiasis, obstructive uropathy, cholelithiasis, and pancreatitis; and EIMs that cannot be categorized clearly in one of the other groups, such as amyloidosis and cancer (7). EIMs involving vascular, hematological, pulmonary, cardiac, and neurological systems probably belong to this last group. Impaired growth, unique to the pediatric age group, may be an EIM potentially related to all of these categories. Iatrogenic EIMs, such as drug-induced bone marrow suppression and corticosteroid-associated myopathy, are not discussed (Table 1).

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PATHOGENESIS

The pathogenesis of EIMs associated with IBD is poorly understood. Many EIMs are hypothesized to be due to immune reactions, supported by the observations that primarily immunological derangements progress to the development of IBD and that patients with IBD have an increased risk of autoimmune diseases (8). Malabsorption, protein-losing enteropathy, fistulas, and intestinal resection each can result in deficiencies of nutrients, proteins, bile salts, vitamins, and minerals with corresponding clinical consequences. Medications used in the treatment of IBD may be associated with many nonintestinal as well as intestinal side effects.

Animal studies support the theory that intestinal bacteria also play a pathological role in the development of EIMs. In HLA-B27 transgenic and T cell receptor-α mutant colitis mouse models, the expression of extraintestinal (and intestinal) disease requires the presence of commensal bacteria; these mouse models do not manifest intrinsic intestinal or extraintestinal pathologies in germ-free environments (9).

Genetic factors also have been implicated in the pathogenesis of EIMs in IBD. Ethnic and racial differences in IBD phenotype have potential implications for diagnosis and management of IBD and its complications (10). Studies reveal associations of EIMs in IBD with major histocompatibility complex loci. For examples, patients with CD who have EIMs are more likely to have HLA-A2, HLA-DR1, and HLA-DQw5, whereas patients with UC and EIMs are more likely to have HLA-DR103, B27, and B58 phenotypes (11,12).

COLITIS-RELATED EXTRAINTESTINAL MANIFESTATIONS

Dermatological Manifestations

Skin involvement has been described in 10% to 15% of patients with IBD (7). The 2 most commonly encountered cutaneous manifestations of IBD are erythema nodosum and pyoderma gangrenosum. Erythema nodosum presents as a single or multiple tender red nodules typically on the extensor surface of the lower extremities. Reported to be more common in CD than UC, erythema nodosum correlates well with and usually reflects increasing bowel activity (1,5,7). Bernstein et al (1) reviewed EIMs in 4445 adult patients with IBD and found prevalence rates of erythema nodosum of 1.9% in patients with CD and UC. A report based on 41 children with IBD found 4 of 32 (12.5%) children with UC and 5 of 9 (56%) with CD had erythema nodosum (5). Several other reports, again, all in adults, report prevalence rates of 2% to 7.5% in CD and 0.9% to 4% for UC (2,7,13–15).

The etiology of erythema nodosum is unknown, although a distinct HLA region on chromosome 6 (HLA-B15) is weakly associated with its development, supporting some genetic influence (12). These lesions usually respond to treatment of the underlying IBD. Although some success has been reported with oral potassium iodide, severe or refractory cases may require systemic corticosteroids or immunosuppressive therapy.

Pyoderma gangrenosum usually begins as an erythematous pustule or nodule that spreads rapidly to adjacent skin and develops into a burrowing ulcer with irregular violaceous edges. Although the appearance can be dramatic, the ulcers are sterile. Lesions are found typically on the extensor surfaces of the extremities, but may appear in other portions of the body, especially sites of trauma. Pyoderma gangrenosum has been reported to evolve from preceding erythema nodosum (16). Pyoderma gangrenosum is reported in 0.5% to 5% of patients with IBD (2,7,15). Most reports suggest that it is more common in patients with UC than those with CD, however, in the study by Bernstein et al (1) of 4445 patients a higher

prevalence was found among patients with CD. Specific prevalence data in children are lacking.

Four distinctive variants of pyoderma gangrenosum are recognized: bullous, familial, malignant, and superficial granulomatous pyoderma. Pyoderma gangrenosum may develop before bowel symptoms, during quiescent disease, or even following colectomy. About 40% of IBD patients with pyoderma gangrenosum develop arthritis (14). Lesions are multiple in the majority of patients, and most appear below the knee. Histological characteristics include lymphocytic vasculitis peripherally in the erythematous zone, neutrophilic infiltration, and a central abscess. Direct immunofluorescence may show immunoglobulin and complement deposits involving superficial and deeper dermal vessels.

Pyoderma gangrenosum often resolves with treatment of the underlying IBD. Mild cases usually respond to local and topical therapy, including intralesional corticosteroid, topical cromolyn sodium, and topical 5-aminosalicylic acid. Effective systemic agents include oral sulfasalazine, dapsone, corticosteroid, and immunomodulators such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil (17). Successful treatment with infliximab in both children and adults has been documented (18,19).

Metastatic CD is a granulomatous dermatitis seen in adults, although isolated cases have been described in children(20). Acute febrileneutrophilic dermatosis (Sweet syndrome) is a rare EIM of IBD and presents as tender, erythematous plaques or nodules involving the arms, legs, trunk, hands, or face (21). It may parallel the intestinal disease or may precede the diagnosis of IBD. Skin biopsies reveal neutrophilic infiltrate with leukocytosis. Azathioprine has been implicated as a possible cause of Sweet syndrome in a patient with CD. Most cases respond to systemic corticosteroids, and metronidazole is reported to be effective in 1 case (22–24). Other cutaneous manifestations associated with IBD include psoriasis, epidermolysis bullosa, polyarteritis nodosa, alopecia, and erythema elevatum diutinum (25,26).

Ophthalmological Manifestations

Ophthalmologic involvement related to IBD is reported in 1.6% to 4.6 % of patients with UC and 3% to 6.3% of patients with CD (2,4,15,27,28). Patients with CD with colonic involvement are more likely to develop ocular problems than those with small bowel disease alone. Data suggest that asymptomatic transient uveitis is common in children with granulomatous bowel disease, but progression to severe adult uveal disease is poorly documented. Ophthalmological changes also may result from treatment rather than directly from the underlying IBD. Involvement of the vascular coats of the eye in IBD may be from bacteria or genetic and immunological factors in the manifestation of extraintestinal symptoms of IBD (29,30).

The most common ocular lesions associated with IBD are episcleritis and uveitis. Episcleritis is characterized by painless hyperemia of the sclera and conjunctiva without loss of vision. Uveitis manifests as an acute or subacute painful eye with visual blurring, photophobia, headache, and iridospasm. Visual acuity is not affected unless the retina or the posterior uveal structures are involved. Diagnosis is made on slit lamp examination, showing flare and cells in the anterior chamber. Acute anterior uveitis is an ophthalmological emergency requiring prompt intervention. Prompt treatment of uveitis with systemic or topical steroids is essential to prevent progression to blindness. Episcleritis rarely progress to blindness if untreated.

Ocular complications also may develop in patients with IBD due to chronic corticosteroid usage. Increased intra-ocular pressures are reported in 22% of pediatric patients exposed to varying doses of corticosteroids (31). The risk of corticosteroid-induced glaucoma leading to irreversible visual loss and corticosteroid-associated cataract should prompt careful ophthalmological evaluation at regular intervals in patients with chronic corticosteroid use. Recent reports of glaucoma also have been noted among children not exposed to corticosteroids, again suggesting an immunological mechanism for its development.

Musculoskeletal Manifestations

The most common EIMs in IBD are musculoskeletal disorders. Spondyloarthropathy is reported in 5% to 20% of patients with IBD (7,15,27,28,32). The 2 patterns described in both children and adults are a peripheral arthritis, sometimes referred to as "colitis arthritis," and the axial form, "ankylosing spondylitis" or "sacroiliitis" (33). The peripheral arthropathy associated with IBD has been subclassified into 2 distinct types. Type 1 is pauciarticular arthritis. It affects fewer than 5 joints, is asymmetrical, and typically affects large joints (knee, elbow, and ankles). It usually manifests with acute self-limiting episodes lasting a median of 5 weeks. Approximately 20% to 40% of all patients have more than 1 episode of arthritis. In one of the few early reports in children (n = 41), 5 of 32 (16%) with UC and 2 of 9 (22%) with CD had arthritis (5). The risk of developing peripheral arthropathy appears to increase with the extent of colonic disease. It also is increased in association with disease complications or other EIMs including abscesses, perianal disease, erythema nodosum, stomatitis, uveitis, and pyoderma gangrenosum. In contrast, type 2 peripheral arthropathy is polyarticular, involving 5 or more joints, more typically the small joints. Polyarticular arthritis with IBD is independent of intestinal disease activity but has been associated with uveitis (12). Symptoms of polyarticular arthritis are reported to persist for a median of 3 years. The development of articular manifestations in patients with UC appears to be influenced by genetic factors present in some major histocompatibility complex haplotypes (34). Type 1 peripheral arthritis is associated with HLA-B27, HLA-B35, and HLA-DR, whereas type 2 is associated with HLA-B44.

Axial arthropathy, both spondylitis and isolated sacroiliitis, is less frequent than peripheral arthropathy and is reported in 3% to 25% of patients (7,15,27,28). As with polyarticular disease, axial arthropathy does not parallel IBD disease activity. Ankylosing spondylitis is reported in 5% to 10% of patients with IBD; most are young (adolescents and young adults) and most are HLA-B27 positive. Ankylosing spondylitis in the HLA-B27-positive patients has a disease course that is identical to ankylosing spondylitis seen in the spondyloarthropathies. Patients with ankylosing spondylitis often experience severe onset of back pain associated with morning stiffness or exacerbated by periods of rest. Symptoms usually are unrelated to the underlying IBD disease activity. Radiographs in early stages may be normal or show only minimal sclerosis.

Peripheral arthropathy usually responds to medical and surgical treatment of the underlying colitis. Other treatment modalities include rest, physical therapy, and intraarticular steroid injections. Nonsteroidal anti-inflammatory drugs used in the management of IBD-associated peripheral arthropathy require caution because of the reported association of exacerbation of IBD and their use, although ongoing studies will provide updated information regarding this controversial issue (35). In contrast to peripheral arthropathy, which usually responds to treatment of colitis, medical or surgical therapy of the underlying IBD does not alter the progressive nature of the axial arthropathy. Other medical therapies have included sulfasalazine, mesalamine, methotrexate, azathioprine, and anti-tumor necrosis factor therapy with infliximab or thalidomide (36).

Osteoporosis/Osteopenia

Osteoporosis and osteopenia have been reported in 23% to 59% of adult patients with IBD (37,38). Osteopenia was observed in 41% of children with CD and in 25% with UC (6). In a study of 42 children, bone-mineral disturbances were found in 57% of cases, with predominance of osteopenia among patients with UC (24%) and osteoporosis among those with CD (24%) (39). In another study of 90 children (50 girls) with IBD (34 free of steroids, 53 treated with steroids, and 3 with unknown usage) and 50 controls (27 girls), the rate of osteoporosis was 8% in girls and 20% in boys, similar to adult reports. A similar proportion of osteoporosis is reported in non–steroid-treated (12%) and steroid-treated (11%) patients (40).

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration leading to increased bone fragility and susceptibility to fracture. Bone density can be estimated using bone densitometry (eg, dual energy x-ray absorptiometry). The densimetric criteria for bone loss are based on t and z scores, which are standard-deviation scores expressed in relation to reference values in young healthy subjects (t score) or sex- and age-matched healthy controls (z score). Osteopenia is defined as a score of -1 to -2.5, and osteoporosis is a score lower than -2.5.

The pathogenesis of osteopenia or osteoporosis in IBD is not well understood. Several factors may interfere with bone promotion and accelerate bone destruction in patients with IBD. Important potential pathogenetic factors in IBD include hypogonadism induced by IBD, manifestation with absence of menses in women, malabsorption of calcium and/or vitamin D, low body mass index, corticosteroid exposure, and disease activity and related elevation of inflammatory cytokines (41). Patients with CD may develop osteoporosis or osteopenia even without treatment with corticosteroids.

Patients with CD should undergo baseline bone densitometry scans, with follow-up imaging studies variably recommended 1 to several years later. With a family history of osteoporosis, bone densitometry should be done sooner and more often. Bone densitometry has been recommended at 1- to 2-year intervals for pediatric patients with long-term, high-dose exposure to corticosteroids, although even adult patients with corticosteroid treatment equivalent to a relatively low dose of 7.5 mg of prednisone for 6 months' duration also may develop significant bone loss and should be monitored carefully (42). Special attention should be directed to ensuring that patients taking corticosteroids have adequate calcium and vitamin D intakes. Prevention of bone loss should begin with an attempt to limit corticosteroid-induced bone loss by minimizing the corticosteroid dosage, substituting with steroid-sparing immunomodulators or adding an agent to enhance bone-mineral uptake. Bisphosphonates and calcitonin have been applied in patients with IBD for the treatment of osteoporosis, although their application in pediatric patients remains to be demonstrated (43).

Osteonecrosis (also referred to as aseptic necrosis or avascular necrosis) is characterized by death of osteocytes, adipocytes, and hematopoietic cells in the bone and eventual bone collapse. It has been described in both children and adults with IBD, with a reported prevalence in 1 series of <1% of all patients and up to 4% of patients taking corticosteroids (44). Early recognition of this potentially serious EIM is important for successful outcome. Diagnosis is made by bone scan and magnetic resonance imaging. Treatment may include medical management (eg, calcium, vitamin D, hydrochlorothiazide, bisphosphonates). Surgical therapies such as core-decompression biopsy and unicompartmental arthroplasty also have been recommended (45).

Oral Manifestations

Oral aphthous stomatitis is seen in at least 5% to 10% of patients with UC and 20% to 30% with CD. Oral lesions may occur before the onset of intestinal symptoms of IBD or may parallel intestinal disease activity. Symptoms include mild discomfort to severe debilitating pain. Biopsies of these lesions often reveal lymphedema and, in patients with CD, granulomata. Treatment with systemic or local corticosteroids or other immunosuppressive medications has been effective.

Pyostomatitis vegetans is a rare, benign, chronic disease characterized by miliary pustules, erosions, and vegetating dermatosis of the skin and oral mucosa. Oral lesions are distinct and appear as multiple pustules with an erythematous base that coalesce and undergo necrosis to form a typical "snail tracks" appearance. Pyostomatitis vegetans has a strong association with gastrointestinal disease and is considered a marker for underlying IBD; most reported cases have been associated with UC. Pyostomatitis vegetans also has been associated with zinc deficiency in a patient with underlying oral CD (46). Management is based on treating the underlying gastrointestinal disease using dietary modification and systemic agents such as antibiotics, sulfasalazine, corticosteroids, azathioprine, and dapsone. Surgical treatment in severe cases of UC involves total colectomy and has resulted in permanent remission of the pyostomatitis vegetans (47).

HEPATOBILIARY MANIFESTATIONS

Hepatobiliary complications are among the more serious EIMs in patients with either UC or CD, and include small bile-duct and large bile-duct inflammation, hepatitis (chronic active, drug induced, granulomatous), cirrhosis, bile-duct carcinoma, fatty liver, amyloidosis, hepatic abscess, and cholelithiasis. The most common serious hepatobiliary complication among pediatric patients is primary sclerosing cholangitis (PSC), a disorder of both intrahepatic and extrahepatic bile ducts (48). Implementation of endoscopic retrograde cholangiopancreatography in children has clarified that much of what was previously labeled as pericholangitis on histology represents small-duct PSC. Data from tertiary referral centers attracting the most affected patients suggest a range of PSC in 1.6% to 7.4% of patients with UC (2,49,50). Olsson et al (51), in a study of 1500 patients 16 years of age and older, reported that the prevalence of the hepatobiliary disease was 5.5% in patients with extensive colitis and 0.5% in patients with distal colitis. A marked male predominance is apparent in patients with colitis and cholangitis compared with those who have colitis without cholangitis.

The etiology of PSC is unknown. The biliary injury may be initiated by an immune-mediated destruction of the hepatobiliary tract caused by transient infection, or the absorption of bacterial products in genetically predisposed individuals with colonic disease. Perinuclear antineutrophil cytoplasmic antibody titers are elevated in many patients with PSC and UC (52). Autoimmune disorders are more frequent in patients with PSC than in patients with IBD without liver disease; 25% of patients with PSC have at least 1 autoimmune disorder outside the liver and colon.

The diagnosis of PSC should be suspected in patients with elevated liver enzymes, specifically the alkaline phosphatase or γ-glutamyl transpeptidase levels. In advanced cases, the total and conjugated serum bilirubin levels are elevated. Serum immunoglobin-G is elevated, anti-smooth muscle and anti-nuclear antibodies are positive, and the HLA DR3, B8 haplotype is found in 70% of patients with PSC. Liver biopsies reveal ductular, portal, and peripheral inflammatory infiltrates, bile-duct proliferation, periductal fibrosis, and varying degrees of bridging fibrosis.

Pharmacological therapies that have been evaluated in adult patients with PSC include prednisone, azathioprine, budesonide, methotrexate, cyclosporine, pentoxifylline, tacrolimus, bezafibrate, and antibiotics. To date, none of these treatments has been shown to affect the course of disease, including patient survival and eventual liver transplantation. Children with PSC experience significant improvements in their liver biochemical indices when treated with ursodeoxycholic acid, but their disease course remains unchanged (53). Transhepatic or endoscopic balloon dilatation and short-term stenting of strictures have provided clinical improvement of symptomatic strictures. Relief of strictures by surgical, endoscopic, or interventional radiological procedures for symptomatic strictures has prolonged survival time. Ponsioen et al (54) reported a 4-year experience with short-term treatment using polyethylene stents for dominant strictures in 32 adult patients with symptomatic PSC for a mean of 11 days. Cholestatic indices improved in 83% of patients at 2 months; 80% remained free of further endoscopic intervention for 1 year and 60% for 3 years. Surgical drainage procedures (eg, portoenterostomy, choledochoenterostomy) are ineffective, are associated with an increased risk of postoperative cholangitis, and may make subsequent liver transplantation technically more difficult. Orthotopic liver transplantation can successfully treat children with PSC, with excellent long-term patient and graft survival (55). Empiric oral vancomycin in children with PSC has shown some improvement in liver enzyme levels (56).

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are relatively common and can slowly progress to end-stage liver disease. NAFLD sensitizes the liver to injury and increases the risk for developing acute or chronic liver failure following another liver injury. CD is a risk factor for developing NAFLD, which can evolve into NASH (57). In a study of Hungarian adult patients with IBD, Lakatos et al (2) found NASH in 9.4% of UC and 19.3% of patients with CD. Another investigation reported NAFLD in 39.5% of CD and 35.5% of patients with UC. The degree of hepatosteatosis was not related to the site, duration, and activity of the disease or the type of medication used (58).

Riegler et al (59) showed a significant association between hepatobiliary abnormalities in both disease duration and steroid and mesalamine treatment in UC patients. Monitoring of hepatobiliary function is important in IBD, even in the absence of symptoms.

Cholelithiasis is more likely a complication of the malabsorption in small intestinal disease and is reported in 11% of adults with CD (4). A recent case-control study in adults suggests that only patients with CD are at higher risk for gallstones compared with UC or matched controls (59 a). In a study of 583 patients with IBD, Stephano et al found that 56 (10.9%) had cholethiasis, of which 41 (13.2%) had CD and 15 (7.5%) had UC. The mechanism of cholesterol-gallstone formation in CD may be related to an abnormal bile lipid composition after ileal resection or disease, and is likely a result of altered enterohepatic bilirubin circulation (60).

IMPAIRED GROWTH

Impaired growth, although also observed in UC, is more common in CD (5,6,61). Low levels of insulin-like growth factor-1 are found in poorly nourished children with CD and growth delay; levels improve with nutritional restitution. In 184 children with IBD with EIMs, Stawarski et al (6) reported growth delay in 28% with UC and 80% with CD. Insulin-like growth factor-1 binding-protein levels are reported to be similar in growth impaired and normally growing children with CD.

Chronic undernutrition is considered the primary pathogenic factor in growth impairment. Diminished oral intake (sometimes simply due to fear of exacerbation of gastrointestinal symptoms), nutrient malabsorption, or a protein-losing enteropathy can contribute to

nutritional deficiencies. Some medications may contribute to under-nutrition. Chronic administration of high-dose daily corticosteroids therapy for as little as 7 to 14 days is associated with diminished type 1 collagen production, a prerequisite for linear growth. Alternate-day corticosteroid regimens appear to have less impact on growth velocity.

Medical therapy is not always successful in reducing disease activity to promote normal growth and development. Recent trials using growth hormone for children with CD show some benefit of this treatment (62). Surgical treatment may be required, and may significantly help children on high-dose corticosteroids with growth retardation. Surgery is curative in UC, allowing discontinuation of growth-suppressive therapies in this group of patients. Surgical intervention in CD, particularly if the disease is limited to a specific and relatively short segment of the intestine, has been shown to induce long-term remission and promote growth in prepubertal or early-pubertal children (63).

EXTRAINTESTINAL MANIFESTATIONS SECONDARY TO COMPLICATION OF OR DIRECT EXTENSION OF BOWEL DISEASE

Genitourinary and Renal Manifestations

Nephrolithiasis, obstructive uropathy, and fistulization of the urinary tract directly result from the underlying disease process. Reported incidence varies from 4% to 23% in adult patients but only in 1% to 2% of children with IBD (4).

Nephrolithiasis is due to calcium oxalate or uric acid stones. Calcium oxalate is due to hyperoxaluria typically associated with either distal ileal CD or ileal resection. Oxalate absorption increases in the presence of unabsorbed fatty acids in the colon. The fatty acids compete with oxalate to bind calcium, displacing the oxalate, which can then be absorbed as unbound sodium oxalate across colonocytes and excreted into the urine. Because sodium oxalate only is absorbed in the colon, calcium-oxalate stones form only in patients with an intact colon. Patients with an ileostomy are prone to formation of uric-acid stones because of frequent dehydration. The sudden onset of severe abdominal, back, or flank pain in patients with IBD, particularly if different from the usual discomfort, should lead to inclusion of a renal stone in the differential diagnosis.

The management of nephrolithiasis in patients with IBD is no different from that in the general population and consists of analgesia, hydration, alkalinization of urine for uric-acid stones, lithotripsy, and surgery. Patients with an ileostomy should be encouraged to drink adequate amounts of fluids.

Urological manifestations in patients with IBD may include ureteral calculi, enterovesical fistula, perivesical infection, perinephric abscess, and obstructive uropathy with hydronephrosis. Ureteral compression is associated with retroperitoneal extension of the phlegmonous inflammatory process involving the terminal ileum and cecum, and may result in hydronephrosis severe enough to cause hypertension. Surgical intervention usually is indicated for obstructive uropathy in patients with IBD. Fistulous disease complicating the urinary tract in patients with CD may present with pneumaturia or recurrent urinary tract infections. Surgical intervention may be required if medical therapy does not heal the fistula. Medical therapy includes azathioprine/6-mercaptopurine or anti-tumor necrosis factor-α agents, such as infliximab or thalidomide (64).

Immune complex glomerulonephritis presenting with proteinuria and hematuria has been described in children and adults with CD or UC (65). Diagnosis is by renal biopsy, and treatment parallels the underlying IBD.

Secondary systemic amyloidosis is a rare but serious complication that has been reported in 0.9% and 0.07% of patients with CD and UC (66,67), respectively. Amyloidosis in patients with IBD often affects the kidney and presents with proteinuria followed by nephritic syndrome and subsequent renal failure or death. Diagnosis is made with liver, rectal, or renal biopsy, although a fat pad aspiration is the most sensitive diagnostic test. Treatment includes colchicine and renal transplantation (68).

Pancreatitis

Pancreatitis may be associated with both UC and CD. The most common cause is iatrogenic and involves sensitivity to medications used to treat IBD (3% of patients), including sulfasalazine, mesalamine, 6-mercaptopurine, and azathioprine. Pancreatitis may present as symptomatic (in 2%) or more commonly asymptomatic (8–21%) disease in adults with IBD. Le Large-Guiheneuf et al (69) reported pancreatitis 27% of pediatric patients with IBD. In a study of 101 children, Stawarski et al (70) reported acute pancreatitis in 4.5% with CD and 5.1% with UC. Pancreatic auto antibodies have been found in up to 40% of patients with CD (71). Further studies are needed to demonstrate whether specific antibodies, apart from their diagnostic relevance for IBD, have a role in its pathogenesis and potentially identifying patients at risk. Diagnosis is confirmed by computed tomography with contrast, magnetic resonance imaging, or endoscopic retrograde cholangiopancreatography.

Hematological Manifestations

Although abnormalities involving all hematopoietic cell lines may be present, anemia is the most common hematological manifestation of IBD. Stawarski et al (6) reported secondary anemia in 5% of patients with UC and 70% with CD. Factors contributing to the development of the various forms of anemia include chronic gastrointestinal blood loss, inadequate dietary iron intake or absorption, vitamin B_{12} malabsorption secondary to terminal ileal disease or ileal resection, folate deficiency due to proximal small-bowel disease or sulfasalazine therapy, or autoimmune hemolysis. Leukocytosis and thrombocytopenia are usually due to immunosuppressant treatments or sulfasalazine. Plasma erythropoietin levels often are lower in patients with IBD than expected, in conjunction with severe anemia. Treatment of anemia depends on the underlying causes. Symptomatic anemia requires blood transfusion, whereas replacement of deficient vitamins may be required in other types. Recombinant erythropoietin has been successfully used in some patients with IBD and refractory anemia.

Thrombocytosis and thromboembolic events resulting from a hypercoagulable state in patients with IBD can lead to pulmonary embolism or thrombosis elsewhere in the body. Thrombosis has been reported in 1.8% of patients with UC and 3.1% of patients with CD. Thromboembolism and thrombosis are less frequently reported among pediatric patients, with 3 patients with UC and 1 with CD described in case reports (72). Factors such as inflammation, fluid depletion, immobilization, surgery, steroid therapy, and use of central venous catheters are prothrombic risk factors in patients with IBD. The development of thromboses may be related to thrombocytosis and an increase in acute-phase reactants during active inflammation. Inflammatory mediators and hypercoagulation are involved in the pathogenesis of IBD, and some proinflammatory cytokines such as interleukin-6 are thrombogenic (73–75). A population-based study in adults suggests that IBD patients have 3-fold greater risk compared with subjects without IBD for developing deep venous thrombosis and pulmonary embolism (76). Factor V Leiden mutation is the most frequent cause of inherited thrombophilia, but studies have shown no difference in the prevalence of Factor V Leiden between patients with IBD and healthy controls. Prevention includes adequate control of disease activity and vitamin supplementation. Medications that affect clotting factors such as warfarin, heparin, and low-molecular-weight heparin have been used

in life-threatening hemorrhage. The risk of intestinal bleeding should always be considered with the use of these medications.

Cardiovascular Manifestations

Children and adults with IBD have been rarely (<1%) reported to develop pleuropericarditis either at initial presentation or during active or quiescent disease (77,78). The pathogenesis of pleuropericarditis is unknown, although certain medications (eg, sulfasalazine and mesalamine derivatives) have been implicated in some cases (79,80). The clinical presentation may include chest pain, dyspnea, or in severe cases pericardial tamponade requiring rapid drainage. Nonsteroidal anti-inflammatory drugs have been used as therapy, although this should be weighed against the hypothetical risk of exacerbating the underlying IBD.

Pulmonary Manifestations

Deterioration of pulmonary function appears to parallel underlying disease activity in patients with IBD. Sulfasalazine-associated lung disease, although rare, is observed after at least 2 months of therapy and includes eosinophilic pneumonia, fibrosing alveolitis, and interstitial pneumonitis. Other pulmonary disorders that have been associated with IBD include pulmonary vasculitis, apical fibrosis, bronchiectasis, bronchitis, bronchiolitis, and granulomatous lung disease. These pulmonary pathological processes do not typically relate to the severity or activity of the underlying IBD. Tuberculosis and other opportunistic infections should be considered in patients taking immunosuppressive medications.

Neurological Manifestations

Central and peripheral neurological disorders are described in patients with IBD and include peripheral neuropathies, myopathies, focal central nervous system defects, convulsions, confusional episodes, meningitis, syncope, optic neuritis, and sensorineural loss (81). Autoimmune mechanisms are proposed for involvement with IBD. Nutritional deficiencies associated with neurological manifestations, such as vitamin B_{12} deficiency, should be investigated. Spinal abscess has been reported in both a child and an adult with initial complaints of severe back pain due to extension of a psoas abscess from the epidural space to the subarachnoid space (82). Careful neurological examination is important in patients developing psoas abscess secondary to CD.

Medications for treatment of IBD also are associated with neurological defects. A greater risk for development of a "stocking glove" peripheral neuropathy is observed with chronic and higher dose metronidazole therapy (83). Although about 50% of patients treated with metronidazole (mean dose, 15–20 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) for ≤6 months develop paresthesias, >80% will have a sensory peripheral neuropathy demonstrated on nerve conduction-velocity testing. Symptoms may persist even after discontinuation of the medication.

SUMMARY

UC and CD commonly manifest signs and symptoms of extraintestinal disease. Patients with evidence of disease extrinsic to the gastrointestinal tract should be considered to have an associated complication of their underlying IBD. Patients with persistent signs or symptoms of EIMs should be evaluated for IBD if not previously diagnosed. Data on EIMs of IBD in children are lacking compared with those in adults (Table 2), and may be revealing in light of recent studies suggesting unique aspects of early-onset IBD compared with older patients (91,92). Information pertaining to the incidence and prevalence of EIMs of IBD in children is essential to improve our understanding of the natural history and associated EIMs in children with IBD.

Acknowledgments

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TABLE 1

Extraintestinal manifestation of inflammatory bowel disease

Colitis-related extraintestinal manifestations

  Dermatological

    Erythema nodosum

    Pyoderma gangrenosum

    Pyostomatitis vegetans

    Psoriasis

    Erythema multiforme

    Epidermolysis bullosa acquista

    Sweet syndrome

    Metastatic CD

  Ophthalmological

    Uveitis/iritis

    Episcleritis

    Scleritis

    Conjunctivitis

    Glaucoma

    Retinal vascular disease

  Musculoskeletal

    Peripheral arthropathy

      Pauciarticular

      Polyarticular

    Axial arthropathy

      Ankylosing spondylitis

    Osteoporosis/osteopenia

  Oral

    Angular stomatitis

    Aphthous stomatitis

    Pyostomatitis vegetans

  Hepatobiliary

    Cirrhosis

    Cholangiocarcinoma

    Steatosis

    Granulomatous hepatitis

    Cholethiasis

    Autoimmune hepatitis

    Hepatic abscess

    Primary sclerosing cholangitis

    Pericholangitis

  Impaired growth

Extraintestinal manifestation secondary to complication of or direct extension of bowel disease

Nephrolithiasis

Obstructive uropathy

Fistula

Gallstones

Pancreatitis

Other

Hematological

Anemia

Leukocytosis

Thrombocytosis

Thrombocytopenia

Coagulation abnormalities

Hypercoagulation disorders

Portal vein thrombosis

Cardiovascular

Pleuropericarditis

Cardiomyopathy

Endocarditis

Myocarditis

Pulmonary

Fibrosing alveolitis

Pulmonary vasculitis

Apical fibrosis

Bronchiectasis

Bronchitis

Bronchiolitis

Tracheal stenosis

Granulomatous lung disease

Abnormal pulmonary function

Neurological

Neuropathy

Myopathy

Meningitis

Seizures

Amyloidosis

Extraintestinal cancer

Acute myelocytic leukaemia

TABLE 2

Prevalence of extraintestinal manifestations of inflammatory bowel disease

Extraintestinal manifestation	Prevalence in adults with IBD	
	UC EIM (%)	CD EIM (%)
Dermatology (2,7)	3.8–19	10.2–23
Erythema nodosum (2,7,13–15,84)	0.9–4	0.7–15
Pyoderma gangrenosum (2,7)	0.5–5	0.8–1.6
Epidermolysis bullosa (85,86)		CR
Sweet syndrome (21,87)	CR	
Uveitis/iritis (2,7)	1.5–4	2–13
Joints/arthritis (2,7)	10.2–26	22.4–39
Ankylosing spondylitis (2,7)	1.5–9	2.7–17
Osteoporosis and osteopenia (7)	9	17
PSC (1,2)	3–12.4	0.4–22.4
NAFLD/NASH (2)	9.4	19.3
Nephrolithiasis (7)	5	5
Amyloidosis (67)	0.7	0.9
Pancreatitis (7)	0.2–0.5	0.4
Anemia (2)	17.7	9.6
Vascular thrombosis (2)	1.8	
Oral aphthous ulcers (2,7)	0.5–4	11
Extraintestinal manifestation	Prevalence in children with IBD	
	UC EIM (%)	CD EIM (%)
Pyoderma gangrenosum (88)	CR[*]	
Joints/arthritis (6)	3.8	–
Osteoporosis and osteopenia (6,39)	24–25	8–41
Growth delay (6)	28	81
Nephrolithiasis (6,89)	3.2	CR
Autoimmune hepatitis (6)	1.3	–
Uveitis (6)	0.63	–
Amyloidosis (90)	CR	
Vascular damage (6)	0.63	4.2
Pancreatitis (6)	2.5	3.9
Anemia (6)	40.5	69

[*]
Except where noted by "CR" (case report) CD total N in children ranges from 21 to 26 and UC total N ranges from 21 to 158.