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• *REVIEW* •

Extraintestinal manifestations in inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBD) can be really considered to be systemic diseases since they are often associated with extraintestinal manifestations, complications, and other autoimmune disorders. Indeed, physicians who care for patients with ulcerative colitis and Crohn's disease, the two major forms of IBD, face a new clinical challenge every day, worsened by the very frequent rate of extraintestinal complications. The goal of this review is to provide an overview and an update on the extraintestinal complications occurring in IBD. Indeed, this paper highlights how virtually almost every organ system can be involved, principally eyes, skin, joints, kidneys, liver and biliary tracts, and vasculature (or vascular system) are the most common sites of systemic IBD and their involvement is dependent on different mechanisms.

Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease

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INTRODUCTION

Inflammatory bowel diseases (IBD) can be really considered to be systemic diseases since they are often associated with extraintestinal manifestations, complications, and other autoimmune disorders. Indeed, physicians who care for patients with ulcerative colitis (UC) and Crohn's disease (CD), the two major forms of IBD, face a new clinical challenge every day, worsened by the very frequent rate of extraintestinal complications. Virtually almost every system can be involved, principally eyes, skin, joints, kidneys, liver and biliary tracts, and vasculature (or vascular system) are the most common sites of systemic IBD and their involvement is dependent on different mechanisms.

Extraintestinal IBD-related immune disease can be classified into two major groups: the first one includes reactive manifestations often associated with intestinal inflammatory activity and therefore reflecting a pathogenic mechanism common with intestinal disease (arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, iritis/uveitis)[1,2] (Table 1); the second one includes many autoimmune diseases independent of the bowel disease that reflect only a major susceptibility to autoimmunity. They are not considered (apart for primary sclerosing cholangitis) as specific IBD features but only as autoimmune associated diseases such as ankylosing spondilitis, primary biliary cirrhosis, alopecia areata, and thyroid autoimmune disease and others[1] (Table 2).

Moreover, many extraintestinal complications due to metabolic or anatomical abnormalities caused directly by

Table 1 Major extraintestinal immune-related manifestations of IBD

Arthritis
Erythema nodosum
Pyoderma gangrenosum
Aphthous stomatitis
Iritis/uveitis

Table 2 Autoimmune disorders associated to IBD

Alopecia areata
Ankylosing spondylitis
Bronchiolitis obliterans
Cold urticaria
Hemolytic anemia
Henoch-Schoenlein purpura
Insulin-dependent diabetes mellitus
Pancreatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Polymyositis
Raynaud phenomenon
Seropositive rheumatoid arthritis
Sjogren syndrome
Thyroid disease
Vitiligo
Wegener's granulomatosis
Takayasu's arteritis

Table 3 Extraintestinal complications in IBD and principal pathogenetic mechanisms of arthritis

Extraintestinal complications in IBD	Principal pathogenetic mechanisms of arthritis
Anemia	Iron deficiency, inflammation
Thromboembolic events	Hypercoagulopathies, platelet activation
Osteopathy	Steroid therapy, vitamin D deficiency inflammation
Growth failure	Malnutrition
Nephrolithiasis	Dehydration, hyperoxaluria, low urinary PH
Cholelithiasis	Intestinal loss of bile acids
Amyloidosis	Acute phase reaction, chronic inflammation
Fatty liver	Malnutrition

IBD have been reported frequently and include osteoporosis, biliary and urinary lithiasis, and anemia (Table 3).

Aim of this paper is to review the pathogenic mechanisms, frequency, features, and therapy of the major IBD-associated extraintestinal manifestations.

Pathogenesis of immune-related extraintestinal manifestation in IBD

Extraintestinal immune-related manifestations in IBD are directly dependent on intestinal disease, often coexist in the same patients and have probably the same, even if not completely clarified, pathogenesis[2]. Evidence coming from many studies in genetically susceptible animal models of colitis suggests the crucial role of enteric flora in activating the immune system against bacterial antigens and contemporary against colonic mucosa on the basis of an antigenic cross-reactivity ("antigen mimicry")[3]. The sharing of these colonic antigens by extraintestinal organs, associated with a genetic susceptibility, would finally lead to an immune attack to these organs[2]. One of the best example is represented by primary sclerosing cholangitis occurring in UC: in a subset of patients, the presence (in sera and colonic mucosa) of anti-colonic mucosa auto-antibodies that cross react with biliary epithelium has been identified[4]. Furthermore, recently a colonic epithelial protein (CEP) and the human tropomyosin isoform 5 (hTM5), which are not only expressed in the colon but also in the biliary tract, skin, eyes, and joints, have been suspected to be the major common targets of autoimmune attack in extraintestinal organs of IBD patients being IgG1 specific auto-antibodies identified in UC patients presenting multiple extraintestinal manifestations[5].

It remains unclear why the extraintestinal organs are not always involved at the same time and why these auto-antibodies are absent in colonic CD. A partial explanation is that genetic factors or local co-existent damage factors (infections, trauma) could regulate the display of cryptic antigens and the susceptibility to autoimmune attack[2].

According to the previously explained mechanism, we can identify an immune induction site, where T cells are primed, represented by the colon and the effectors sites that are the extraintestinal organs. Immune cells infiltrate the effectors sites (where they will proliferate) with the help of adhesion molecules (α4β7 integrin, vascular adhesion protein 1) that have a cytokine-mediated overexpression in specific tissues[6].

It is interesting how autoimmune attack can happen many years after the removal of the colon. In the case of primary sclerosing cholangitis (PSC), probably memory lymphocytes that have been primed in the bowel can recirculate for many years also even after the removal of the colon without causing damage until the occurrence of a stimulus in the liver that activates inflammation with the overexpression of adhesion molecules (MAdCAM and CCL 25) and consequent persistent lymphocytes recruitment[7]. Interference with adhesion molecules could be useful in the treatment of extraintestinal manifestation as it has already been shown for the intestinal inflammatory activity[8].

Genetic susceptibility

Extraintestinal manifestations have certainly a familial predisposition (83% of concordance between siblings)[9] and this suggests the existence of a strong genetic influence leading to the identification of many suspected predisposal genes.

HLA system is considered as one of the major genetic markers associated with IBD and extraintestinal manifestations, probably a specific and appropriate antigen presentation that leads to autoimmune reaction in particular predisposing conditions.

It has been reported that UC patients who display HLA-B8, DR3 phenotype have a 10-fold higher risk of primary sclerosing cholangitis[10].

Moreover, UC patients who have HLA DRB1*0103 (DR103) have a higher risk of ocular and articular manifestations[11] and patients with HLA-B*27 and B*58 have a higher risk of uveitis (Orchard TR 2002). HLA-B*27 is strongly associated with ankylosing spondylitis (AS) being present in 90% of these patients but it seems not to be significantly associated with IBD; anyway IBD patients with HLA-B*27 positiveness have a higher risk to develop AS and IBD patients with axial articular involvement are HLA-B*27 positive from 25% to 75%[12]. The polymorphism -1031 C TNF-α has been associated with erythema nodosum in IBD patients[13]. It is possible that HLA genes interfere actively in the pathogenesis of IBD-extraintestinal manifestations or that are in linkage disequilibrium with other really responsible unknown genes. Moreover, caspase-activation recruitment domain containing protein 15 (CARD15), a gene found in association with ileocecal CD with a potential role in the bacterial handling, has been recently associated with sacroiliitis even if previous results did not agree[14].

Joint involvement in IBD

Inflammatory arthropathies are the most common extraintestinal manifestations in IBD patients with a prevalence ranging between 7% and 25%[1,12]. Articular and musculoskeletal manifestations are included in the spondyloarthropathies (SpAs) that are a group of seronegative autoimmune related disorders with common characteristics including: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease,

some forms of juvenile arthritis and acute anterior uveitis[15].

Articular involvement (peripheral or axial) can precede, be synchronous or begin afterward the diagnosis of IBD, it is characteristically pauciarticular, asymmetrical, transitory, migrating, prevalently non deforming. The axial involvement can vary from asymptomatic sacroiliitis to inflammatory lower back pain to ankylosing spondylitis (that occurs in 3% of IBD patients)[1].

It is interesting that the high incidence of asymptomatic sacroiliitis (varying from 10% to 52%)[16,17,18] and on the other hand the equally high incidence (about 50%) of characteristic inflammatory low back pain in the absence of radiological findings in IBD patients[12] indicating how history and physical examination should be the diagnostic tools. Peripheral arthritis, different from axial involvement, has a significant positive association with the skin, mouth, and ocular manifestation; it happens more frequently in CD (and particularly in colonic localization), often accompanies intestinal activity ameliorating with IBD pharmacological or surgical treatment[1]. In some patients, despite the amelioration of gut inflammatory activity, articular disease persists[19].

Arthritis is often associated with enthesitis, tenosynovitis, dactylitis that can also appear in the absence of arthritis[20]; typically they do not alter inflammatory markers and can compromise deeply the quality of life.

Conventional treatment of inflamed joints include nonsteroidal anti-inflammatory drugs and cyclooxygenase-2-inhibitor that should be used for short-term period because of gastrointestinal side effect and IBD reactivation risk[21,22] nevertheless at drug suspension articular relapse can occur. Also local intra-articular steroid treatment can be useful.

The majority of interventional studies included undifferentiated spondyloarthropathies- or ankylosing spondilytis patients and no IBD patients, so that the results can only be extrapolated. Sulfasalazine has been shown to be effective in peripheral joint disease in SpAs patients[23,24] and positive but limited results have been obtained with methotrexate[25].

Interesting results have been obtained with anti TNF-α inhibitors in resistant SpAs with IBD. In uncontrolled studies, infliximab has shown efficacy in the treatment of SpAs in CD patients as induction and maintenance therapy[26-28], also in the absence of acute phase reactants and intestinal activity; there is also a reported case of positive results in SpA associated with ulcerative colitis[29]. In limited reports (two cases) etanercept, that is ineffective in IBD treatment[30], has given good results in the treatment of SpAs associated to CD[31]. It is not clear at the moment the effect of anti TNF-α therapies on articular damage evolution, certainly the early recognition and appropriate treatment can help to limit the patient's inability.

Hepatobiliary disease

Hepatobiliary diseases are common in IBD patients; they can or cannot be immuno-mediated and can also depend on side effects of medications (see Table 4). Elevation of liver function tests have been observed from 11% to 49% in IBD patients in observational studies[32-34]. The most common immuno-mediated hepatobiliary disease is primary sclerosing cholangitis (PSC) that is a chronic cholestatic disorder characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. It is more frequent in male individuals, and the prevalence of IBD (mostly UC) in PSC is about 70-80%[35]. Conversely about 2-7% of UC patients[35,1] and 0.7-3.4% of MC patients have a diagnosis of PSC[36,1]. Suggestive symptoms of PSC are fatigue, pruritus, jaundice, and abdominal discomfort but it is not rare that the isolate finding of abnormalities in liver biochemical markers (first of all alkaline phosphatase); in fact 15-70% of PSC patients are asymptomatic[37,1]. There are no specific auto-antibodies and so biopsy or cholangiography is often necessary for the diagnosis. In PSC patients, IBD frequently present some specific features: pancolonic extension with rectal sparing, backwash ileitis, low intestinal activity, and high pouchitis incidence after colectomy. These distinguishing features have suggested the existence of an IBD-PSC specific clinical phenotype[38]. It is well-known that the increased risk of colonic dysplasia/carcinoma in PSC patients compared to the general population (10-fold risk)[39] and to other UC patients[35] it could depend on the long-lasting and asymptomatic colitis (consequently often underestimated) and by alterations in bile salts pool or folate deficiency. Similarly it has significantly increased the risk of bile duct cancer[40] and metabolic bone disease[41,38]. PSC has a median survival time of 9-12 years from the time of diagnosis; it seems that neither concomitant IBD presence nor colectomy (in UC patients) alter its natural history. Moreover, the colorectal cancer risk does not seem to be decreased after liver transplantation[42].

The therapeutic possibilities in PSC are limited; the best results have been obtained with UDCA at a high dose (until 20 mg/kg)[43-45] and the combined use of corticosteroids showed only a little additive benefit[46,47].

The best clinical approaches to PSC include colonoscopic examination with a biopsy to identify a possible asymptomatic UC and/or cancer and a prevention colonoscopy program in patients identified to have had UC. Association between primary biliary cirrhosis (PBC) and UC is rare but possible and it has been reported in 15 cases; similarly to the CSP it seems that colectomy does not alter the progression of the hepatic disease[48].

Apart from classical immunological liver diseases in IBD patients, they are often observed for other abnormalities. Liver enlargement is the most common reported finding and is strictly related to steatosis grade. Steatosis has been described in more than 30% of patients and it does not seem to be related to the kind of IBD and sex. Data about the influence of disease activity and pharmacological treatment on steatosis are contradictory[49].

Also cholelithiasis is more frequent in IBD patients (about 10%) than in the general population (7%) and mainly in CD (first of all in ileal localization); it seems

to correlate with female sex, previous surgery (mainly ileal resection), and old age. In limited series, it has been shown to be less often symptomatic than in the general population[49]. Probably cholelithiasis is caused by bile salt pool alteration for malabsorption.

Rare complications reported in literature are liver abscesses; it is thought that in most cases portal bacteremia, favorite by mucosal barrier alterations, can be the principal mechanism; rarely an ascending acute cholangitis in PSC has been suspected to be the cause[50]. Portal vein thrombosis and suppurative pylephlebitis has also been described in rare cases[49].

Cutaneous manifestations

Cutaneous manifestations of IBD are relatively common. The incidence varies from about 10% at the time of IBD diagnosis to more than 20% in the course of the disease[1]. Skin lesions can be classified into three principal classes: granulomatous, reactive, and secondary to nutritional deficiency.

Granulomatous cutaneous lesions have the same histological features of the bowel disease and include: perianal and peristomal ulcers and fistulas, metastatic CD, oral granulomatous ulcers.

Perianal disease is very frequent occurring in about 50% of CD patients during their clinical history, and it varies from perianal erythema to abscesses and perianal complex fistulae[51].

Other fistulae can be internal or entero-cutaneous; rarely develop on the abdominal scar of laparotomy or at the umbilicus. Many efforts have been made to treat fistulizing disease, and the classical surgical approach has been supported recently by a larger use of drugs. Antibiotics, azathioprine/mercaptopurine, tacrolimus, thalidomide showed efficacy in uncontrolled studies[52] but at the moment only infliximab showed effectiveness as induction[53] and maintenance therapy[54] in phase III controlled trials; consequently it has been approved as first line therapy in perianal and enterocutaneous fistulizing CD by the United States Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products in Europe. Surgical procedures as colostomy in the more severe cases of perianal fistulas, fistulotomy, abscesses drainage, and non-cutting setons placement seem to be very useful, and the combined medical and surgical approach is probably the best one[55].

Metastatic CD is a rare complication defined as the occurrence of specific granulomatous cutaneous lesions remote from the intestinal disease[56]. It manifests as subcutaneous nodules or ulcers mainly at the lower extremities with rare case of genital (testicular and vulvar) localizations. It seems unrelated to the bowel activity. Corticosteroids, antibiotics, azathioprine, methotrexate[57], and more recently infliximab[58,59] have been used successfully.

The group of reactive skin manifestations of IBD includes aphthous stomatitis, erythema nodosum, pyoderma gangrenosum, and the rare Sweet's syndrome.

Aphthous stomatitis is observed in about 10% of patients: it occurs generally during active intestinal disease, often recurs and shows a good response to intestinal treatment.

The prevalence of erythema nodosum in IBD is 3-8%. It appears more often in women, in the colonic localization, in concomitance with arthritis and active intestinal disease[1]; furthermore, there is a positive response to proctocolectomy[42].

Histological examination shows lympho-histiocytic infiltrate of the lower derma. On the basis of uncontrolled data, corticosteroids are generally an effective therapy; also immunosuppressive therapy is used[56]. Resistant cases have been treated effectively with infliximab[60].

Pyoderma gangrenosum is a very debilitating ulcerating chronic skin disorder occurring in about 1-2% of IBD patients. It occurs often on the extensor surface of the legs, particularly in coincidence with exacerbation of intestinal disease and in association with other extraintestinal manifestations (arthritis and erythema nodosum)[1,61]. Moreover, it is often associated with colonic involvement and in UC patients it seems to benefit lesser than erythema nodosum from colectomy[42].

According to disease severity, the treatment (based on non-controlled evidence) can be local or systemic and includes a high dose of oral or intralesional corticosteroids, immunosuppressive/immunomodulatory therapy (cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, dapsone)[61]. Infliximab has shown to be very effective in the refractory disease and can be used as first choice therapy[59,62,63]; also etanercept has been reported to be effective in a refractory case of pyoderma gangrenosum[64].

Another rare cutaneous manifestation associated with IBD is the Sweet's syndrome. It is a neutrophilic dermatosis probably related to pyoderma gangrenosum consistent with painful erythematous plaques or nodules often associated with fever and leukocytosis that usually responds to corticosteroids[65].

The more frequent nutritional-deficient cutaneous manifestation is the acrodermatitis enteropathica; it is caused by zinc deficiency and manifests as a psoriasis form erythema[61].

Furthermore, an association between autoimmune cutaneous disease and IBD has been reported. The most frequent disease is psoriasis (7-11% of IBD population *vs* 1-2% of general population) than vitiligo and more rarely are polimyositis, lupus erythematosus and scleroderma[66].

Ocular manifestations of IBD

Ocular manifestations occur in about 10% of IBD patients. They can be immune-related (episcleritis, scleritis, uveitis, corneal disease) or related to drug exposure (cataract, glaucoma).

Episcleritis manifests as acute redness, irritation, burning, tender to palpation; if there is also an impairment of vision, the presence of a scleritis is possible. In this case, a referral to an ophthalmologist is mandatory for risk of vision loss. Uveitis can be anterior and posterior and is often associated with joints and skin manifestations.

Anterior uveitis is the most common and presents painful eye, visual blurring, and photophobia but can be also asymptomatic and sometimes precedes the diagnosis of IBD. Concomitance with IBD activity is typical for episcleritis and uveitis[1,67].

Corneal disease (potential cause of perforation) has also been reported; conjunctivitis is frequent in IBD population but probably does not differ in frequency and etiologic factors from the general population. Anyway it is important that the clinician is aware that serious ocular disease can mimic conjunctivitis in IBD patients[67].

Ocular manifestations can benefit first of all by the treatment of the underlying IBD (particularly for anterior uveitis and episcleritis).

Treatment of ocular disease can prevent complications such as retinal detachment or optic nerve swelling in scleritis and secondary glaucoma and cataracts in uveitis.

Cycloplegics, NSAIDs, topical and systemic steroids are useful. Immunosuppression can be necessary in case of scleritis; sulfasalazine/mesalazine seems to prevent anterior uveitis recurrence[67]. Recently infliximab has shown efficacy in acute uveitis, in episcleritis, and scleritis[68,69]. Other rare reported ocular manifestations of IBD are: retinitis, orbital IBD, retinal arterial and venal occlusion, optic neuritis, retinal vasculitis, marginal corneal disease, lid margin ulcers[70,67].

Metabolic osteopathy

IBD is also associated with an increased risk of osteoporosis and osteopenia. The prevalence rates ranges from 2% to 30% for osteoporosis and from 40% to 50% for osteopenia[71]. The risk of fractures in IBD patients varies widely in different studies[72-74] (from an OR of 1.41 to 2.5) the real impact being completely clear on the IBD population; because of contrasting results, it is also uncertain if the risk is comparable for UC and MC and for men and women.

Osteoporosis occurrence is often underestimated as shown in an observational study conducted in the UK[74] in which women aged 65 years with severe IBD have shown a 10-years probability of hip fracture of 7%; nevertheless only 13% of patients who had already sustained a fracture were in bone-sparing therapy.

Furthermore, a significant number of fractures in IBD patients (as in the general osteoporotic population) are asymptomatic (14.2% in a study of Stockbrugger) and many fractures will be underreported[75].

Bone loss and consequent fractures are certainly multifactorial processes. They are significantly dependent on the age (above 60 years), the use of corticosteroids[74-76] and the grade of systemic inflammation (intestinal disease activity correlates with the risk of fracture)[74].

Recently the role of the inflammatory-induced osteopenia has been revaluated and a surface receptor (RANK) localized on osteoclasts that induces osteoclastogenesis has been identified. Its ligand (RANKL) is induced by proinflammatory cytokines; its decoy receptor that prevents ligation of RANKL to RANK is called osteoprotegerin (OPG), and is produced by osteoblasts and prevents bone loss. Its production is inhibited by corticosteroids and increased by bisphosphonates. So OPG-RANKL-RANK system is certainly a pivot in inflammatory-induced bone loss[77,78]. Initial therapeutical use of recombinant OPG in inflammation-induced osteoporosis seems to be promising[79].

On the basis of these findings, the role of nutritional deficiency could be smaller than previously thought, as also shown in a preliminary recent observational study that found low intake of calcium (<1 000 mg/die) and vitamin D (<200 IU/die) in premenopausal IBD women not to be a predictor of bone loss[80].

Other factors that could favor osteoporosis are the use of corticosteroids, the hypogonadism, and the immobility. Also genetic markers have been proposed as determinants of bone loss in IBD patients. In the future, they could contribute to identify high-risk patients and support clinical behavior[81].

Definition of a correct clinical approach is difficult because therapeutic trials on IBD patients with the specific end-point of fractures prevention are lacking and an extrapolation by the major clinical trials on osteoporosis is difficult, since these studies involve postmenopausal patients, certainly older than IBD patients with osteoporosis.

A small randomized, placebo-controlled trial showed that alendronate significantly ameliorates spine bone density compared with the control group after 1-year-long therapy in IBD patients[82]. Also azathioprine, effective on intestinal activity, seems to have positive effect on bone loss retardation[83].

The expert recommendations on therapy, in the absence of more specific evidence, do not significantly differ from that of the general population. Supplementation of vitamin D for patients above 60 years, therapy with bisphosphonates in case of osteoporosis (identified with densitometry), osteoporotic fractures and chronically steroid treatment, use of minimum dosage of corticosteroids (preferentially non-systemic), correction of early menopause or male hypogonadism by hormone therapy have also been reported[84,85]. Recently apart from OPG use, another osteoanabolic substance, the parathyroid hormone 1-34, is under evaluation for the steroid-induced osteoporosis[86]; in the future they could show effectiveness in IBD osteoporosis. More efforts are yet to be taken in the identification of high-risk patients and in the definition of the most cost-effective clinical behavior in IBD patients.

Thromboembolism and IBD

Patients with IBD have a well-known increased risk (threefold higher than in controls) of thromboembolism (TE), which is an important cause of morbidity and mortality. The incidence ranges from 1.2% to 6.1% according to different studies and in necropsy studies it reaches 39%[87].

Thrombosis accidents occur prevalently as deep vein thrombosis and pulmonary thromboembolism; they happen in earlier age than in non-IBD patients and are more frequent in active or complicated IBD; the type of

IBD and the sex seems not to influence thromboembolic risk[87,88]. Using the logistic regression model, it has been found that IBD is an independent risk factor for thrombosis that is a specific IBD feature. In fact, other inflammatory chronic condition as rheumatoid arthritis or chronic intestinal malabsorptive conditions as celiac disease do not show an increased risk of TE[87].

IBD patients have a frequent exposure to classical thrombosis risk factors: immobility, surgery, steroid therapy, central venous catheter, contraceptives/hormone substitution, smoke; nevertheless, these risk factors do not explain the TE risk increase completely[87].

It is well-known that in IBD patients there is not a completely explained imbalance between coagulation and fibrinolysis in favor of coagulation.

Active intestinal inflammation is not probably the unique risk determinant since about 30-40%[87,89] of thrombosis occurs during quiescence of the IBD and proctocolectomy has not shown a very clear protective effect on recurrent venous thrombosis[90].

Also other factors have been claimed; hyperhomocysteinemia, a well-known risk factor for venous and arterial thrombosis, occurs more often in IBD patients than in the general population and seems to be directly dependent by folate and vitamin B12 deficiency even if there is not a complete concordance in literature[91-93].

The role of the inherited thrombophilia has been recently reviewed[94]. The analysis has shown that the most frequent prothrombotic genetic mutations (factor V Leiden mutation, G20210A mutation in the gene of prothrombin, homozygous in the gene of methylenetetrahydrofolate reductase) are not significantly associated with IBD.

At the same time with the limit of a small number of subjects participating in the studies, it seems that there is no difference in the prevalence of genetic mutations in IBD patients with thrombosis compared with non-IBD subjects with thrombosis. Anyway a recent study comparing IBD patients with thrombosis and IBD controls has revaluated the role of genetic factors finding a significant higher prevalence of factor V Leiden in the thrombosis group (20% *vs* 0%)[95].

The data regarding the prevalence of antiphospholipid antibodies in IBD are conflicting, but seem to suggest an increase frequency in IBD. In limited series, the level of lipoprotein (A) has been found to be higher than in controls[87]. No evidence exists about treating thrombotic events differently than in non-IBD patients[87].

Conclusively many factors are suspected to play a role in the thromboembolic increased risk of IBD patients but further studies are necessary to identify their specific contribution.

At the moment in IBD patients the elimination of removable risk factors is recommendable; in case of thrombosis probably is useful to evaluate the thrombotic risk performing coagulation laboratory parameters and genetic tests.

Anemia

Anemia is a frequent extraintestinal manifestation in IBD; about one-third of IBD patients have hemoglobin levels below 12 g/dL[96]. The anemic state correlates strictly with the quality of life and so is certainly an important problem in the therapeutic management of chronic patients[97]. Multiple pathogenic mechanisms often coexist in anemic patients leading to mixed features anemia. Chronic intestinal bleeding with iron loss (due to bowel inflammation) causes a hypochromic and microcytic anemia with associated hypoferremia and hypoferritinemia; the chronic inflammatory disease (typically characterized by hyperferritinemia) can cause anemia through the proinflammatory cytokine-dependent diversion of iron traffic to reticuloendothelial system and erythroid progenitor cell development interference[98]. The same inflammatory cytokines are able to inhibit erythropoietin production[99]. Recently, *in vitro* anti-TNF-α factors showed positive effects in preventing apoptosis of erythroid cells[100]. Other mechanisms implied in anemia are iron malabsorption (in duodenum or upper jejunum disease CD), vitamin B12 malabsorption (in terminal ileum and gastric CD), and folate deficiency (malabsorption, inadequate diet, and side effects of sulfasalazine and methotrexate). Vitamin B12 and folate deficient anemia is characteristically macrocytic. Myelosuppressive direct effects have been reported frequently for azathioprine/6-mercaptopurine and sometimes also for sulfasalazine and 5-aminosalycilic acid[101]. Correction of the anemic state is useful also in low-grade anemia. It is important to prevent and treat intestinal flares that are often the cause of anemia and to reintegrate the lacking of iron, B12, and folate.

In low-ferritin patients, prevention therapy with oral iron can be sufficient; in overt anemia iron intravenous (preferentially iron sucrose) supplementation should be preferred to oral route because of major efficacy and no collateral intestinal side effect. Epo therapy is useful in patients with no satisfactory response to iron therapy alone[101]. Low levels of Epo, soluble transferring receptors or transferrin have shown to predict iron sucrose resistance[102].

Urinary system manifestations

IBD is a risk factor for renal immune and non-immune mediated diseases.

The prevalence of nephrolithiasis in IBD varies from 2% to 6% and is more frequent in CD than in UC[103]. Calcium-oxalate stones are the most common and are caused by hyperoxaluria due to increased intestinal absorption of oxalate. In fact in the bowel that does not absorb fatty acids link calcium preventing calcium-oxalate precipitation with the consequent increased absorbable oxalate fraction. More than one lithogenic factors are often present in the same patient, more frequently during active disease. The main lithogenic risk factors are: low urinary volume, low urinary PH, increased excretion of lithogenic substances as oxalate, phosphate, uric acid, and decreased concentration of anti-lithogenic substances as citrate and magnesium. Colectomy in UC and ileo-colonic resection in CD seems to further increase the risk of lithiasis and oxalate stone formation occurs mainly in ileal CD[104].

Table 4 Drugs and their possible adverse side effects

Drugs	Possible adverse side effects
Corticosteroids	Acne, fluid retention, fat redistribution, hypertension, hyperglycemia, psycho-neurological disturbances, cataracts, growth failure in children, osteonecrosis[115]
Mesalazine	Nausea, dyspepsia, rare nephritis, rare idiosyncratic worsening of IBD[116]
Sulfapyridine	Headache, nausea, anorexia, rare hypersensibility hepatitis, hemolytic anemia, pancreatitis, reversible sperm abnormalities, worsening of IBD[116]
Azathioprine/mercaptopurine	Pancreatitis, bone marrow suppression, hepatotoxicity[115]
Methotrexate	Nausea, leucopenia, hepatic fibrosis, hypersensibility pneumonia[117]
Cyclosporin	Nephrotoxicity, hypertension, headache, gingival hyperplasia, paresthesias[115]
Tacrolimus	Nephrotoxicity[115]
Infliximab	Infusion reactions, delayed hypersensitivity-like reactions, drug-induced lupus, tuberculosis reactivation[118]
Metronidazole	Nausea, metallic taste, peripheral neuropathy[115]

Periodic sonographic examination is recommended for early diagnosis and for the prevention of complications. Furthermore, minimal signs of tubular damage have been found in about 20% of IBD patients but rarely they are clinically relevant[105].

A calculus uretheral obstruction, prevalently localized on the right, is also possible and is related to the mechanisms of adherence and compression by inflamed bowel (prevalently terminal ileum)[103]. Urinary tract fistulas occur in about 1.7-7.7% of patients. They can cause pneumaturia, dysuria, recurrent infections, and fecaluria. At the moment in most cases, the non-satisfactory response to medical therapy makes surgery the best option[106].

Clinical relevant renal amyloidosis has been reported in about 1% of IBD patients (more frequently in ileal CD). It is probably related to acute phase reaction proteins[107]. In IBD patients, cases of glomerulonephritis causing nephrotic syndrome and renal failure have also been reported. They are related to intestinal disease activity, are quite responsive to IBD therapy and can present many patterns at histology[108]. Moreover, it seems that mi nimal, clinically non significant, glomerular inflammatory changes are quite frequent in IBD patients as shown in a post mortem study (70% of subtle renal lesions *vs* 8% of controls)[109] but following data do not exploit this aspect.

Other rare extraintestinal manifestations

It has been reported in literature about the occurrence of other rare extraintestinal manifestations of IBD, such as, chronic recurrent multifocal osteomyelitis (CRMO), myositis[110], polyneuropathy, Guillain-Barre syndrome[111], lymphocytic encephalomyeloneuritis[112], myocarditis[113], and pleuropericarditis[114].

Drug-induced side effects

Many drugs used in IBD treatment can cause side effects involving various organs (Table 4). These effects that often need drug interruption enter in differential diagnosis with extraintestinal manifestations/complications of IBD; their early diagnosis is facilitated by periodical serum analysis exploring liver, pancreatic, renal, and hematological system integrity as for example is recommended in methotrexate and azathioprine use[115]. Furthermore, the limited use to short period of other drugs can prevent their effect as for example as it often happens for corticosteroids (Table 4).

CONCLUSION

IBD is a systemic disease, since its clinical manifestations can affect not only the bowel but also practically any other organ (eyes, liver, osteoarticular system, kidneys, and so on) through different (often not completely cleared) mechanisms. At the moment, awareness of the high incidence of extraintestinal manifestations is often inadequate. Therefore, prevention, early diagnosis, and adequate treatment of these pathological conditions, sometimes more dramatic than the intestinal disease, are necessary to increase patients' health. Clinical interventional trials in IBD patients should consider these conditions with more attention to indicate the best cost-effective method for clinicians.

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