EXTRA INTESTINAL MANIFESTATIONS AND COMPLICATIONS IN INFLAMMATORY BOWEL DISEASE

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EXTRAINTESTINAL MANIFESTATIONS AND COMPLICATIONS IN INFLAMMATORY BOWEL DISEASE (Abstract). Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), doesn't affect only the intestinal tract, but also involve other organs such as: eyes, skin, joints, liver and biliary tracts, kidneys, lungs, vascular system. It is difficult to differentiate the true extraintestinal manifestations from secondary extraintestinal complications. The pathogenetic autoimmune mechanisms include genetic susceptibility, antigenic display of autoantigen, aberrant self-recognition and immunopathogenetic autoantibodies against organ-specific cellular antigens shared by colon and extra-colonic organs. An important role is owned by microbes due to molecular mimicry. This paper reviews the frequency, clinical presentation and therapeutic implications of extraintestinal symptoms in inflammatory bowel diseases. **Keywords:** INFLAMMATORY BOWEL DISEASE, ULCERATIVE COLITIS, CROHN'S DISEASE, EXTRAINTESTINAL MANIFESTATIONS

Ulcerative colitis (UC) and Crohn's disease (CD) are systemic disorders that often involve other organs such as joints, skin, eyes, lungs, biliary tract or urinary system . The etiology is unknown. The main characteristic is an increase of pro-inflammatory cytokines levels: IL-1,-6,-8, tumor necrosis factor (TNF)-α, a decrease of anti-inflammatory interleukins: IL-6,-10 and an increased recruitment of leukocytes to the area of inflammation.

Ulcerative colitis has a chronic intermittent course with periods of remission and relapse. Inflammation is limited to the colon mucosal layer and affects the mucosa in a retrograde and continuous way. An immune mediated mechanism determines an inappropriate immune response against intraluminal antigens affecting individuals who are genetically predisposed. According to the distribution of the inflammation at the mucosal layer, the Montreal Classification was made (tab. I).

TABLE I

Montreal classification of UC

E1	Proctitis (inflammation limited to rectum)
E2	Left-sided disease/procto-sigmoiditis (colorectum distal to splenic flexure)
E3	Extensive disease/pancolitis (proximal to splenic flexure)

Crohn's disease is a chronic relapsing IBD. It is characterised by transmural granulomatous inflammation often involving the ileoceacal part of the gut and leading to a stricturing or even fistulising disease. The ethiology is unknowm, but it was seen an inadequate response of the immune system to the gut microbiota in genetically predisposed people.

The Montreal classification divides CD in three categories according to the localization of the inflammatory process (tab. II).

TABLE II

Montreal classification of CD

Age	Localization	Course of the disease
< 16 years	ileal	Inflammatory
17-40 years	colonic	Stricturing
> 40 years	Ileo-colonic	Penetrating

Prevalence of extraintestinal manifestations (EIM) oscillates between 6-47% of IBD patients (1). In most of the cases they follow the clinical course of gut inflammation, but also may not correlate with disease activity. Some studies suggested an autoimmune reaction regarding an isoform of tropomyosin (Tropomyosin related peptide) detected in skin, joints, eye, biliary epithelium and gut (2) and a common genetic background, HLA system being one of the major genetic markers associated with IBD and EIM. There is a correlation between CD and HLA-A2,-DR1, DQW5 and between UC and HLA-DRB1*0103, B27, B58 (3, 4). Also the genetic ground can guide about the risk of extraintestinal manifestations (tab. III) (3, 5, 6).

TABLE III

HLA system and the risk of EIM

HLA- B8, DR3	primary sclerosing cholangitis
HLA- DRB1*0103 (DR103)	ocular, articular manifestations
HLA B27, B58	uveitis
HLA B27	ankylosing spondylitis
1031 C TNF-α	erythema nodosum
CARD 15, NOD2 gene	sacroiliitis

TABLE IV

Classification of EIM

Extraintestinal immune-related manifestations of IBD	• arthritis • erythema nodosum • pyoderma gangrenosum • aphtous stomatitis • iritis/uveitis	• the same pathogenic mechanism • associated with intestinal inflammatory activity
Autoimmune disorders associated to IBD	• ankylosing spondylitis • primary sclerosing cholangitis • polymyositis • primary biliary cirrhosis • alopecia areata • thyroid disease	• major susceptibility to autoimmunity • independent of IBD
Extraintestinal complications	• osteoporosis • biliary/urinary lithiasis • anemia • tromboembolic events • amyloidosis • fatty liver	• metabolic or anatomical abnormalities due to IBD • inflammatory activity • medication use • poor nutrient intake/absorption

Extraintestinal manifestations can be devided in three categories: extraintestinal immune-related manifestations of IBD, autoimmune disorders associated to IBD and extraintestinal complications according to the pathogenic mechanism and the relation between intestinal inflammatory activity and the presence of this secondary disorders (tab. IV) (7).

1. **Musculoskeletal manifestations**

Inflammatory arthropathies are the most common extra-intestinal manifestations of IBD and take part of a wider group named spondylarthropathies. Joint manifestations can precede, be synchronous or can manifest afterward IBD.

Peripheral arthropathies appear can pre-date the onset of the gut clinical signs. Their prevalence in UC is smaller (5-10%) than in CD (10-20%) (8). The main characteristic is their non-erosive, non-deforming pattern. *Type1***:** pauci-articular (less than five joints) is defined by migratory non-deforming and non-erosive large-joint arthropathy predominantly of the lower limbs. It is associated with HLA B27, -B35, HLA-DRB1-0103 in up to 65% of the patients. The acute episode is self limiting (mean duration is 5 weeks) and runs in parallel with the IBD. *Type 2***:** polyarticular (more than five joins affected) characterised by symmetrical persistent small joint poly-arthropathy. The course is independent of the underlying IBD and can last for several months (8). The genetic background is strongly correlated with HLA B44, MHC class I chain-like gene A (on chromosome 6) (4, 9).

The etiology is based on genetic predisposition and the exposure to luminal bowel contents. It has been demonstrated a dysbiosis with a decreasing quantity of bifidobacteria, lactobacilli, *Escherichia coli*, an increase of facultative flora (*Staphylococcus, Klebsiella*, *Proteus*), a modification of the colonocyte's cell receptor maturity of mucus (decreased staining intensity by lectins) and a cytokine imbalance with an increase of proinflammatory markers (IL-1,6,8, TNF α) (10).

Axial arthropaties are not correlated with disease activity of IBD. Sacroiliitis is non-progresive and is not associated with HLA B27. This form is associated with enthesitis, tenosynovitis, dactylitis even in the absence of arthritis (11). Bacteria and bowel inflammation plays a decisive role in the pathogenesis of IBD-associated ankylosing spondylitis, fact demonstrated by ileocolonoscopy in patients with idiopathic spondylarthropathies (12).

Osteoporosis is an extraintestinal complication of IBD. The main role in the ethiopathogenesis is assumed to the connection between OPG-RANKL-RANK (13). Osteoclastogenesis is induced by a surface receptor (RANK) located on osteoclasts. Its ligand (RANKL) is induced by proinflammatory cytokines. On the other hand, osteoblasts produce osteoprotegerin (OPG) which prevents ligation of RANKL to RANK, so the bone loss is stoped. It has been proved that alendronate improved spine bone density in IBD patients (14).

Osteomalacia is also a complication of IBD. It is determined by a prolonged and severe vitamin D deficiency. Often appear after multiple intestinal resections in severe cases of CD (15).

2. **Hepatobiliary manifestations**

It can or cannot be related to immunological disorders or may depend on side effects of therapy used for IBD.

Primary sclerosing cholangitis (PSC) is a chronic, slowly progressive cholestatic

disorder characterized by inflammation and fibrosis of intrahepatic / extrahepatic bile ducts. 2-7% of patients with UC develop PSC. It is a premalignant condition for cholangiocarcinoma and determine a higher risk of colonic dysplasia/carcinoma due to folate deficiency, long periods and asymptomatic colitis or changes in bile salts (16, 17). High titres of autoantibodies to neutrophils (pANCAs) were found in the serum of these patients (18) and also they have, in a proportion of 70%, HLA DR3, B8 haplotype.

Hepatobiliary complications include: cholelithiasis, more frequent in CD and caused by the malabsorption of bile salts from the inflamed terminal ileum, fatty liver due to steroid therapy or poor nutrition, liver abcesses, portal vein thrombosis, suppurative pylephlebitis.

3. **Mucocutaneous manifestations**

Mucocutaneous manifestations can be divided in three classes of injuries relaying on the ethiopathogenic mechanism (tab. V).

TABLE V

Classification of mucocutaneous manifestations

Granulomatous disorders	• perianal/peristomal ulcers and fistulas • metastatic CD • oral granulomatous ulcers
Reactive skin manifestations of IBD	• aphthous stomatitis • pyoderma gangrenosum • erythema nodosum • Sweet's syndrome
Nutritional- deficient cutaneous manifestations	• acrodermatitis enteropathica

Granulomatous lesions and IBD have the same histological pattern. Perianal / peristomal ulcers and fistulas frequently appear in patients with CD (50%) and can be external or internal (entero-cutaneous) (19). In the group of external manifestations we can find: perianal erythema, abscesses and perianal complex fistulae. Internal fistulas are more serious and require a prompt systemic medication and even surgery. Metastatic CD are represented by subcutaneous nodules or ulcers which appear especially at the lower limbs (20). Oral lesions are aphthous ulcers which appear in 10% of patients with UC and in 20-30% in those suffering from CD.

Reactive skin manifestations of IBD usually are diagnosed in parallel with intestinal disease activity. *Aphthous stomatitis* follows the colonic localization of IBD. The histological pattern show a lymphohistiocytic infiltrate located in the lower derme. The disease can be associated with arthritis and correlated with IBD acuteness.

Pyoderma gangrenosum may run an independent course of the underlying IBD activity. Commonly involves the skin with a predilection for the lower limbs, but also may occur around surgical stomata or in any area of the skin. Macroscopically it is represented by discrete pustules which coalesce and form ulcerations with central necrosis and with erythematous or violaceous edges. Histologicaly there is a deep suppurative folliculitis with diffuse neutrophilic infiltration and dermolysion. It can exist in association with other extraintestinal manifestations such as arthritis, ery-

thema nodosum (21). *Erythema nodosum* appears as raised, warm, tender erythematous nodules tipically in the pre-tibial areas. Histologicaly it is a septal panniculitis due to immune complex deposition. It was proved a genetic association between erythema nodosum and a certain HLA region of chromosome 6 (HLA B) (22). Flares occur concurrently with gut exacerbations. The disease normaly heals without ulcerations and resolve spontaneously within 3-6 weeks. *Sweet's syndrome* is a neutrophilic dermatosis which appears as painful erythematous nodules or plaques. It is often associated with fever and leukocytosis.

Nutritional - deficient cutaneous manifestations include acrodermatitis enteropathica determined by zinc deficiency. It has a clinical pattern as a psoriasis erythema.

4. **Ocular manifestations**

There are two kinds of manifestations depending on their immunopathogeny. Immune-related conditions such as: episcleritis, scleritis, uveitis, corneal disease or related to drug exposure: cataract, glaucoma (table VI). A high risk for developing these conditions is the presence of genotypes HLA B27, B58, DRB 10103. Usually are flaring and subsiding at the same time as the bowel inflammation (22, 23) (tab. VI).

TABLE VI
Classification of eye disorders

immune-related ocular manifestations	• episcleritis • scleritis • uveitis • corneal disease
ocular manifestations related to drug exposure	• cataract • glaucoma

Episcleritis is the most common extraintestinal manifestation, mainly in CD patients. It appears at the same time with active gut disease. Clinically we can find acute redness, irritation, burring, tender to palpation. The treatment refers to topical steroids and also the therapy of the underlying intestinal condition.

Uveitis appears more common in females and more often bilaterally. It may not parallel gut disease activity and sometimes can precede the diagnosis of IBD. It need a prompt therapy because can lead permanent damage to the eye.

Corneal disease includes ***conjunctivitis*** which is quite frequent.

Use of steroids can lead to ***cataract*** and the malabsorption of vitamin A can determine ***keratopathy*** or ***night blindness***.

5. **Pancreatic manifestations**

Pancreatic manifestations can take two forms: acute or chronic pancreatitis. Acute pancreatitis is induced by drugs such as salycilates, azathioprine, 6-mercaptopurine. Usually it has a mild course with a remission of the inflammatory processes after discontinuing the therapy. In 40% of CD patients were found pancreatic autoantibodies (24). Chronic pancreatitis is characterized by a decreased exocrine function due to circulating inflammatory mediators or to autoantibodies against pancreatic tissue (25, 26). Patients with IBD have modifications of intrapancreatic duct (26).

6. Thromboembolic events

Thromboembolic events have an incidence between 1.2% to 6.1%, but some necropsy studies found out that this incidence is much higher being up to 30% (27). The pathogenesis refers to hyperhomocysteinemia due to the deficiency of vitamin B_6, B_{12} (malabsorption) or folate (malabsorption, use of folate-inhibiting drugs such as methotrexate/ sulfasalazine) (28). One study found a significant higher prevalence of factor V Leiden in the group of IBD patients (29). Other events which participate at the procoagulatory status are: an increase frequency of antiphospholipid antibodies, higher levels of lipoprotein (A) (27).

7. **Anemia**

Anemia is considered to have many pathogenic ways: chronic intestinal bleeding, iron malabsorption in duodenum and upper jejunum, vitamin B12 malabsorption, folate deficiency due to malabsorption or to side effects of drugs. Also the high level of proinflammatory cytokines can make a diversion of iron traffic to reticuloendothelial system (30). A lot of drugs used for the treatment of the current gut disease can have direct myelosuppressive affect (sulfasalazine, azathioprine, 6-mercaptopurine) (30).

8.**Urinary system manifestations**

IBD patients present quite frequent minimal, subclinical, glomerular inflammatory changes. Interstitial nephritis and tubular proteinuria is often attributed to CD (31). Glomerulonephritis can lead to nephrotic syndrome and renal failure and is directly related to the activity of the bowel disease. Urinary complications include nephrolithiasis and urinary tract fistulas. Nephrolithiasis appear more frequent in CD than in UC (32). The most common are calcium-oxalate stones due to fat malabsorption that cause a lack of free calcium and increased oxalate absorption.

Renal amyloidosis appers more often in ileal CD. The ethiology is unclear, but is related to chronic inflammation and acute phase reaction proteins (33).

9. **Pulmonary manifestations**

Usually pulmonary disease parallels the bowel intestinal activity. The most common manifestation is bronchial inflammation and suppuration with or without bronchiectasis. The etiopathogeny includes: the same embryological origin of the lung and gastrointestinal system by ancestral intestine (34), similar immune systems in the pulmonary and intestinal mucosa (35), the presence of circulating immune complexes and auto-antibodies.

Half of patients with CD have ***subclinical alterations*** of the lungs without pulmonary symptoms (36). Abnormal pulmonary function tests are found in 42% of IBD patients without respiratory symptoms or radiograph findings (37). Lung inflammation correlates with bowel disease activity.

Airway diseases include upper-airway obstruction, tracheobronchitis, chronic bronchitis, granulomatous bronchiolitis, bronchiectasis, asthma and acute respiratory failure. The most frequently appear bronchiectasis (37). Bronchoscopy shows diffuse inflammation of the trachea and bronchi and the biopsy reveals metaplastic disorders in the epithelium and granulomatous infiltration.

Lung parenchymal diseases include bronchiolitis obliterans with organizing pneumonia (BOOP), unspecified interstitial lung disease, noncaseating granulomatous inflammation and fibrosis, parenchymal nodules and granulomata, alveolitis and alveolar consolidation. The lung biopsy shows acute alveolitis, granulomatous lymphocytic infiltration of the interstitium and

of the walls of small arteries with slight interstitial fibrosis.

Pleural diseases include pneumothorax, pleural thickening, pleuritis and pleural effusion (38). There is an association between pleural effusion and pericarditis (39). The pleural complications of CD may run an independent course and may be present at the time of inactive bowel disease.

Drug-related lung disease can be interpreted as complications. Sulfasalazine and mesalamine can induce interstitial disease, eosinophilic pleuritis/ pneumonia or even asymptomatic lung injury(40). After the use of azathioprine or 6-mercaptopurine has been reported interstitial pneumonitis, BOOP, chronic pneumonitis /fibrosis and pulmonary edema (41). Methotrexate can cause interstitial pneumonitis, granuloma formation and bronchiolitis (42). Biological therapy with anti TNF drugs (infliximab, adalimumab, certolizumab) is associated with the presence of opportunistic infections due to the suppression of T cell-mediated immunity or can directly affect the lung parenchyma causing acute respiratory distress syndrome, diffuse alveolar hemorrhage, nonbronchiolitis inflammatory nodular pattern of the lung and interstitial lung disease. Frequently appear or is reactivated latent tuberculosis (43).

10. **Cardiovascular manifestations**

Heart involvement is rare. It is seen more frequently in men and in those with ulcerative colitis. These manifestations are not related to the activity of the bowel disease. Cardiac involvement may present as pericardial effusion, myopericarditis and conduction defects. Pericarditis is the most common manifestation in CD.

Other patients with Crohn's disease or ulcerative colitis suffer from vasculitis. There is a relation between Takayasu's arteritis and Crohn's disease due to cross-reacting antibodies against gut mucosa and aortic tissue. Some patients developed thrombotic complications by activating the coagulation system and it manifest like atrial thrombi, embolism of the pulmonary arteries, myocardial infarction and disseminated intravascular coagulopathy. Furthermore, a few cases were reported about atrio ventricular blocks, amyloidosis of the heart, dilative cardiomyopathy and endomyocardial fibrosis in patients with chronic inflammatory bowel disease (44).

11. **Neurological manifestations**

It includes central and peripheral nervous system involvement. Peripheral neuropathy is one of the most common complications. It has also been found an inflammatory myopathy. Cranial neuropathies include the Melkersson-Rosenthal syndrome, optic neuritis, and sensorineural hearing loss (45-47). Ischemic stroke depends on few mechanisms, including large/small artery disease, paradoxical embolism, endocarditis, vasculitis. Thrombosis of the dural sinus and cerebral veins are as frequent as arterial stroke in IBD. Multiple sclerosis has been frequently associated with IBD (48). Almost 50% of IBD patients have asymptomatic white matter lesions. Other central nervous system manifestations are represented by: a slowly progressive myelopathy, epidural and subdural spinal empyema, seizures and encephalopathy (49, 50).

CONCLUSIONS

Beside the classic gastrointestinal manifestations, a large number of IBD patients present with extraintestinal manifestations which can affect every site of the body. Extraintestinal manifestations may produce greater morbidity than the underlying intes-

tinal disease and may even be the initial presenting symptoms of the IBD. Some of these disorders are more frequent associated with active colitis (joint, skin, ocular and oral manifestations), others are related to small bowel dysfunction (cholelithiasis, nephrolithiasis, and obstructive uropathy) and few are nonspecific manifestations (osteoporosis, hepatobiliary disease, and amyloidosis). The distinction between disease and treatment side effects can be extremely difficult and may sometimes be impossible. Early recognition of these extraintestinal manifestations should help guide therapy that will reduce overall morbidity in affected patients.

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