EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASES

Andra Consuela IONESCU [*]
Mircea DICULESCU[1]
Cosmin CIORA[2]
Lucian IONESCU[3]

ABSTRACT:
INFLAMMATORY BOWEL DISEASES (IBD) CROHN'S DISEASE (CD) AND ULCERATIVE COLITIS (UC), ARE CHRONIC INFLAMMATORY DISORDERS OF UNKNOWN ETIOLOGY THAT APPEAR IN GENETICALLY PREDISPOSED SUBJECTS, IN RESPONSE TO ENVIRONMENTAL FACTORS, MICROBIAL AGENTS, INTESTINAL IMMUNE SYSTEM. ULCERATIVE COLITIS AND CROHN'S DISEASE ARE ASSOCIATED WITH A VARIETY OF EXTRAINTESTINAL MANIFESTATIONS, THEREBY THEY CAN BE CONSIDERED SYSTEMIC DISEASES. THE MOST COMMON MANIFESTATIONS AFFECT THE MUSCULOSKELETAL AND DERMATOLOGIC SYSTEM. OTHER SITES ARE EYES, HEPATOPANCREATOBILIARY TRACT, KIDNEYS. ANEMIA IN IBD IS MULTIFACTORIAL IN ORIGIN, CHRONIC AND RECURRENT MANIFESTATION, THAT AFFECT PATIENT'S QUALITY OF LIFE. PATIENTS HAVE AN INCREASED RISK OF THROMBOEMBOLISM, REQUIRING THROMBOPROPHYLAXIS. WE PRESENT IN THIS LITERATURE REVIEW THE EXTRAINTESTINAL MANIFESTATIONS THAT ASSOCIATE WITH INFLAMMATORY BOWEL DISEASE.

KEY WORDS: EXTRAINTESTINAL MANIFESTATIONS, INFLAMMATORY BOWEL DISEASE, SYSTEMIC DISORDER, INFLAMMATION

INTRODUCTION

Inflammatory bowel disease, Crohn's Disease (CD) and Ulcerative Colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract of unknown etiology, that appear in genetically susceptible individuals exposed to environmental risk factors. They are characterised by remisions alternating with exacerbation periods.

Crohn's Disease shows chronic transmural inflammation, that can affect any segment of the digestive tract. The inflammation is asymmetric, segmental and discontinuous[4].

[*] MD. PhD Student, Department of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest, andra_cristocea@yahoo.com
[1] Prof. PhD, Department of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest
[2] MD. PhD, Department of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest
[3] MD. MS, Radiology, Central Military Hospital, Bucharest
[4] Gheorghe Liana, Gheorghe Cristian, " Bolile inflamatorii intestinale idiopatice" "Vademecum in gastroenterologie", ed. Nemira 2002

Ulcerative Colitis is chronic inflammation strictly localised at the colon, never progressing above the ileocecal valve. In contrast to CD, in UC is affected only the mucosa, and the lesions are continuous.

The annual incidence of CD was 12.7/100.000 person-years in Europe, 5.0/100.000 person-years in Asia and the Middle East, and 20.2/100.000 person-years in North America. The annual incidence of UC was 24.3/100.000 person-years in Europe, 6.3/100.000 person-years in Asia and the Middle East, and 19.2/100.000 person-years in North America.

The prevalence in Europe for UC is 505/100.000 persons, for CD is 322/100.000 persons, and in North America for UC is 249/100.000 persons and for CD is 319/100.000 persons[5].

Diseases show a first peak between 15 and 25 years , and a second one between 55 and 65 years.

The Jewish population is highly susceptible to these diseases. Regarding race, CD and UC are 2-5 times more frequent in Caucasians than in African-American population.

Inflammatory bowel diseases can be considered systemic diseases because multiple organs can be affected: bones, joints, skin, eyes, lungs, kidneys, hepatobiliary system. These are called extraintestinal manifestations (EIM). What causes these extraintestinal manifesations it is unknown, but it is considered that all these manifesations are an abnormal response from the immune system. When the immune system reacts it triggers inflammation in others organs.

These EIM can appear prior to, during or after the active episode of the disease, and have an overall prevalence of 25-40% of IBD patients.

Aproximately 35% of IBD patients have Extraintestinal Manifestations (EIM).

25% of IBD patients have more than 1 EIM, and that increases the risk of developing a second EIM[6]. A retrospective survey of 500 IBD patients, conducted in the Department of Gastroenterology and Hepatology - Fundeni Clinical Institute is presented in Table 1[7].

Table 1. Prevalence of EIM among patients with Crohn Disease (CD), Ulcerative Colitis (UC), Indeterminate colitis (IC). Retrospective study on 500 IBD patients included in IBDProspect

EIM	CD	UC	IC
Arthritis	32	16	2
Sacroileitis/Ankylosing spondilitis	19	10	1
Erythema nodosum	7	4	0
Pyoderma gangrenosum	1	1	0
Pericholangitis	0	0	0
Uveitis/Episcleritis	6	1	1
Oxalate kidney stones	5	9	0

[5] Natalie A. Molodecky, Ing Shian Soon, Doreen M. Rabi, William A. Ghali, et al, "Increasing Incidece and Prevalence of the Inflammatory Bowel Disease With Tine, Based on Systematic Review", Gastroenterology 2012;142(1):46-54

[6] Levine S. Jonathan, Burakoff Robert, **"**Extraintestinal Manifestations of Inflammatory Bowel Disease" ,Gastroenterol Hepatol (N Y). 2011 Apr; 7(4): 235–241

[7] Andra Ionescu, Razvan Iacob, Cristina Cijevschi, Adrian Goldis et al, "Extraintestinal manifestations (EIM) in Inflammatory bowel disease: a retrospective survey" (paper presented at the National Congres of Gastroenterology, Hepatology and Digestive Endoscopy, Iasi, June 11-13, 2015)

EIM	CD	UC	IC
Renal Amyloidosis and Ureterohidronephrosis	1	0	0
Lingering urinary tract infections	7	0	1

Musculoskeletal manifestations:

The most common EIM of IBD are musculoskeletal manifestations, ocuring in 9-53% of IBD patients, and they are considered to be part of the seronegtive spondyloarthropathies.

Peripheral arthritis is divided into type 1 and 2. Type 1 peripheral arthritis affect less than 5 large joints, is acute and associated with active bowel disease. Type 2 affect 5 or more small joits, is chronic, symmetrical and is not associated with the activity of IBD[8].

Axial arthropathies, Sacroilitis and Ankylosing spondylitis, are seen in IBD and are unrelated with disease activity. They represent the inflammation of the spine and sacroiliac joints, manifested by pain and stiffness in the low back, relieved with exercise and worse in the morning.

Disease location may influence risk: patients with colonic involvment in Crohn's Disease and extensive colitis are more likely to develop musculoskeletal complications.

The diagnosis of joint-related complications in IBD is based on the clinical symptomatology and the exclusion of other intestinal disorders that are associated with joint manifesations like: Celiac Disease, Behcet Syndrome, Whipple's Disease. It is recommended to do radiographyes of the spine and sacroiliac joints or Computer Tomography, to show the chronic changes in the Ankylosing spondylitis and Sacroilitis, like syndesmophytes and sacroiliac erosions.

Osteoporosis:

Osteoporosis can occur in patients with IBD because of the disease progress and also because of the treatment used such as corticosteroids.

The patients have an elevated risk of fracture compared with general population.

It is recommended for patients who used corticosteroids for >3months duration to undergo bone mineral density scan.

Dermatologic manifestations:

Most common skin complications of IBD are represented by Erythema nodosum and Pyoderma gangrenosum. Other skin lesions include Psoriasis, Oral aphtous stomatitis, Sweet syndrome.

Erythema nodosum is an inflammatory disease manifested by the appearance of reddish nodules located on the front of the legs below the knees[9].They are warm, painfull, slightly higher than the surrounding skin. The lesions appear when the intestinal disease is active, and frequently resolve when bowel disease subsides. Treatment is for the underlying IBD.

Pyoderma gangrenosum is an inflammatory disease characterised by neutrophilic infiltration of the dermis and destruction of the tissue. It begins with a pustule or nodule that

[8] Evans E. Paul, MD, Pardi S. Darrell, MD., "Extraintestinal Manifestations of Inflammatory Bowel Disease: Focus on the Musculoskeletal, Dermatologic, and Ocular Manifestations", Medscape Gastroenterology, March 19, 2007

[9] IBDClinic, "What is IBD? What are extra-intestinal manifestations of IBD?", http://www.ibdclinic.ca/what-is-ibd/

breaks and form an ulcer, covered with pus or necrotic debris. After it is healed leaves a typical cribriform scarring. The legs are most commonly affected, but it can appear in any part of the body[10].

Sweet syndrome is an acute febrile neutrophilic dermatosis, manifested by fever and painful skin lesions that appear on arms, face, back, neck. The cause isn't always known, in some cases it may appear after an infection, illness, medications.

Hepatopancreatobiliary manifestations:

Hepatopancreatobiliary manifestations of IBD include Primary Sclerosing Cholangitis (PSC), Steatosis, Cholelithiasis, Portal vein thrombosis, Pericholangitis, drug-induced hepatotoxicity, and others.

One of the most important complication is PSC, that is a chronic cholestatic disease, characterised by stricturing, inflammation and fibrosis of medium and large intrahepatic and extrahepatic bile ducts. It' an immune-mediated chronic hepatic disease with uncertain etiology[11].

PSC has a strong connection with IBD, especially with UC. Almost 75% of patients suffering from PSC have also UC. Only 5-10% of PSC patients have CD. On the other hand, only 5% of UC patients and 2% of CD patients develop PSC.

Symptoms of PSC are fatigue, jaundice, abdominal pain, pruritus. Biopsy or cholangiography is necessary for the diagnosis.

There are some clinical features that suggest the presence of IBD in a patient suffering from PSC: pancolonic extension, low intestinal activity, backwash ileitis.

The risk for colonic cancer is increased because of the long term asymptomatic colitis, also PSC is a major risk factor for developing cholangiocarcinoma.

Cholelithiasis is frequently seen in IBD patients, especially in CD patients with ileal localisation. It correlates with female sex, old age, previous surgery. It represents one of the most common surgical problems worldwide. Ileal resection predispose to the formation of pigment stones[12].

Portal vein thrombosis, described in rare cases, is a blockage or narrowing of the portal vein by a blood clot. Most people have no symptoms, but in some people it may appear Portal Hypertension. Doppler ultrasonography confirm the diagnosis, the blood flow through the portal vein is reduced or absent[13].

In Pericholangitis, the patients are most of the time asymptomatic, the elevated level of alkaline phosphatase suggests the disease. The diagnosis is histologically, and characterised by destruction of small bile ducts, mononuclear inflammatory infiltrate and fibrosis.

Ocular manifestations:

The most common ocular complications are Episcleritis, Uveitis, Scleritis.

Episcleritis is the inflammation of the episcleral tissue. It appears parallel with intestinal activity, patients with an active flare and acute redness and burning in one or both eyes should be suspected.

It resolves with treatment for IBD.

[10] Rowe A. William, Anand BS, "Complications of Inflammatory Bowel Disease", Medscape, May 11, 2015

[11] Danese Silvio, Semeraro Stefano, Papa Alfredo, Roberto Italia, et al, "Extraintestinal manifestations in inflammatory bowel disease",World J Gastroenterol 2005 December 14;11(46):7227-7236

[12] University of Connecticut Health Center, Diseases of the Gallbladder, http://fitsweb.uchc.edu/student/selectives/Luzietti/Gallbladder_cholelithiasis.htm

[13] Orfanidis T. Nicholas, "Portal Vein Thrombosis", Merck Manual/Liver and Gallblader Disorders/Blood Vessel Disorders of the Liver, http://www.merckmanuals.com/home/liver-and-gallbladder-disorders/blood-vessel-disorders-of-the-liver/portal-vein-thrombosis

Scleritis is a chronic, painful, potentially blinding disease, characterised by edema, celular infiltration of the scleral and episcleral tissue.

Requires agressive treatment with steroids or immunosupresants and control of the IBD in order to prevent a recurrence.

Arthritis, uveitis and erythema nodosum is the most common triad. Uveitis is four times more common in women. The appearance is not parallel to IBD.

Clinical suspicion should be in any patient with ocular compaints and other extraintestinal manifestations. The eye is painfull and red, the vision is blurred, patients have photophobia. Topical and systemic steroids are necessary.

All these diseases are immune related, but there are treatments that may cause ocular pathology. Steroid can lead to cataract and glaucoma.

Renal manifestations:

Calcium oxalate stones are the most common and are caused by hyperoxaluria due to increased intestinal absorption of oxalate. They appear more frequent in Crohn's patients with disease of the small intestine than in the general population.

Surgery in IBD like colectomy in UC or ileo-colonic resection in CD increase the risk of lithiasis. Oxalate stone formation appear especially in ileal CD.

Amyloidosis is a rare and severe extraintestinal manifestation, associated with CD. It doesn't react to the intestinal treatment and leads to kidney failure. Is more frequent in ileal CD.

Urinary tract infections often occur in IBD[14],[15],[16].

People with inflammatory bowel disease are at higher risk for blood clots, especially Deep Venous Thromboembolism, secondary to the activation of coagulation factors and trombocitosis.

Anemia is a frequent extraintestinal manifestation. About one third of IBD patients have hemoglobin levels below 12g/dl.

Hypocromic and microcytic anemia, with hypoferremia and hypoferritinemia is caused by intestinal bleeding. Chronic inflammation can cause anemia with hyperferritinemia. Other mechanism by wich anemia cand appear is iron malabsorbtion in duodenum and upper jejunum CD, vitamin B12 malabsorbtion in gastric and terminal ileum CD, and folate malabsorbtion because of improper diet or side effects of Sulfasalazine and Methotrexate.

Fistulas are abnormal connections formed between the bowel and other organs. There are entero-cutaneous fistulas, entero-enteric fistulas, entero-vesicular, entero-vaginal and perianal fistulas.

CONCLUSION

Extraintestinal manifestations of inflammatory bowel diseases affect almost every organ , that's why IBD can be considered a systemic disorder. EIM have high incidence in

[14] Trinchieri A., Lizzano R, Castelnuovo C, Zanetti G, et al, "Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease", Arch Ital Urol Androl. 2002 Jun;74(2):61-4

[15] Crohn's & Colitis Foundation os America, "Extraintestinal Complications: Kidney Disorders", January 30, 2009, http://www.ccfa.org/resources/kidney-disorders.html

[16] Varda BK, McNabb-Baltar J, Sood A, et al, "Urolithiasis and urinary tract infection among patients with inflammatory bowel disease: a review of US emergency department visits between 2006 and 2009", Urology. 2015 Apr;85(4):764-70. doi: 10.1016/j.urology.2014.12.011. Epub 2015 Feb 7

both CD and UC. Prevention, early diagnosis and proper treatment are necessary to improve patients lives.[17]

"ACKNOWLEDGEMENT: This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531".

Affiliation to UMF " Carol Davila".

[17] Vavricka SR, Scharl M, Gubler M, Rogler G1, "Biologics for extraintestinal manifestations of IBD", Curr Drug Targets. 2014;15(11):1064-73

REFERENCES

1. **Gheorghe Liana, Gheorghe Cristian, "** Bolile inflamatorii intestinale idiopatice" "Vademecum in gastroenterologie", ed. Nemira 2002
2. **Natalie A. Molodecky, Ing Shian Soon, Doreen M. Rabi, William A. Ghali, et al,** "Increasing Incidece and Prevalence of the Inflammatory Bowel Disease With Tine, Based on Systematic Review", Gastroenterology 2012;142(1):46-54
3. **Levine S. Jonathan, Burakoff Robert, "**Extraintestinal Manifestations of Inflammatory Bowel Disease" ,Gastroenterol Hepatol (N Y). 2011 Apr; 7(4): 235–241
4. **Andra Ionescu, Razvan Iacob, Cristina Cijevschi, Adrian Goldis et al, "**Extraintestinal manifestations (EIM) in Inflammatory bowel disease: a retrospective survey" (paper presented at the National Congres of Gastroenterology, Hepatology and Digestive Endoscopy, Iasi, June 11-13, 2015)
5. **Evans E. Paul, MD, Pardi S. Darrell,** MD., "Extraintestinal Manifestations of Inflammatory Bowel Disease: Focus on the Musculoskeletal, Dermatologic, and Ocular Manifestations", Medscape Gastroenterology, March 19, 2007
6. **IBDClinic,** "What is IBD? What are extra-intestinal manifestations of IBD?", http://www.ibdclinic.ca/what-is-ibd/
7. **Rowe A. William, Anand BS**, "Complications of Inflammatory Bowel Disease", Medscape, May 11, 2015
8. **Danese Silvio, Semeraro Stefano, Papa Alfredo, Roberto Italia, et al, "**Extraintestinal manifestations in inflammatory bowel disease",World J Gastroenterol 2005 December 14;11(46):7227-7236
9. **University of Connecticut Health Center,** Diseases of the Gallbladder, http://fitsweb.uchc.edu/student/selectives/Luzietti/Gallbladder_cholelithiasis.htm
10. **Orfanidis T. Nicholas,** "Portal Vein Thrombosis", Merck Manual/Liver and Gallblader Disorders/Blood Vessel Disorders of the Liver, http://www.merckmanuals.com/home/liver-and-gallbladder-disorders/blood-vessel-disorders-of-the-liver/portal-vein-thrombosis
11. **Trinchieri A., Lizzano R, Castelnuovo C, Zanetti G, et al,** "Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease", Arch Ital Urol Androl. 2002 Jun;74(2):61-4
12. **Crohn's & Colitis Foundation os America, "**Extraintestinal Complications: Kidney Disorders", January 30, 2009, http://www.ccfa.org/resources/kidney-disorders.html
13. Varda BK, McNabb-Baltar J, Sood A, et al, "Urolithiasis and urinary tract infection among patients with inflammatory bowel disease: a review of US emergency department visits between 2006 and 2009", Urology. 2015 Apr;85(4):764-70. doi: 10.1016/j.urology.2014.12.011. Epub 2015 Feb 7
14. **Vavricka SR, Scharl M, Gubler M, Rogler G1,** "Biologics for extraintestinal manifestations of IBD", Curr Drug Targets. 2014;15(11):1064-73