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Complications of Ulcerative Colitis in Children

Sabina Wiecek

Abstract

Inflammatory bowel disease is a group of chronic disorders of the gastrointestinal tract, including Lesniowski-Crohn disease, ulcerative colitis, and indeterminate colitis. The most frequently occurring symptoms in patients with IBD, including ulcerative colitis, involve abdominal discomfort, recurring and often bloody diarrhoea, weight loss, and the resulting anaemia and/or cachexia. Extraintestinal manifestations of ulcerative colitis may precede the diagnosis of inflammatory bowel disease, they may also occur during remission (pyoderma gangrenosum, uveitis, spondylitis, and PSC) or accompany an exacerbation of the disease (erythema nodosum, episcleritis, aphthae, and some forms of peripheral spondyloarthritis). This study focuses on the most common extraintestinal manifestations and complications in ulcerative colitis in paediatric patients.

Keywords: ulcerative colitis, parenteral symptoms, complications, children

1. Introduction

Inflammatory bowel disease is a group of chronic disorders of the gastrointestinal tract, including Lesniowski-Crohn disease, ulcerative colitis, and indeterminate colitis. The course of these disorders is characterised by alternating periods of remission, which may last even a few years, and exacerbation. Chronic inflammatory bowel diseases develop as a result of coexisting genetic, immunological and environmental factors, and the immune system, which is linked to the digestive system and constitutes a vast proportion of the whole defence mechanism of our body. Among the most frequently occurring symptoms in patients with IBD, including ulcerative colitis, are abdominal discomfort, recurring and often bloody diarrhoea, weight loss, and the resulting anaemia and/or cachexia. The aspects of extraintestinal symptoms of inflammatory bowel diseases are not discussed often, and yet in as many as 40–50% of patients, at least one extraintestinal manifestation of IBD occurs with even 25% of patients reporting two or more symptoms not related to the digestive system. The causes of the occurrence of extraintestinal symptoms in the course of ulcerative colitis have been widely discussed. Increased permeability of the intestinal wall allows for the contents of the bacterial wall (endotoxins) and other components to enter the bloodstream, which may cause inflammation. Extraintestinal manifestations of ulcerative colitis may precede the diagnosis of inflammatory bowel disease, occur during remission (pyoderma gangrenosum, uveitis, spondylitis, and primary sclerosing cholangitis)

The skeletal system	Osteopenia/osteoporosis
The liver and bile ducts	Steatosis Primary sclerosing cholangitis Autoimmune cholangitis Bile duct cancer
Joints	Arthritis of the large joints Sacroiliitis Ankylosing spondylitis
The skin	Erythema nodosum Pyoderma gangrenosum
The eye	Conjunctivitis Iritis
The vascular system	Vein thrombosis Embolism

Table 1.
Extraintestinal symptoms of ulcerative colitis.

or accompany an exacerbation (erythema nodosum, episcleritis, aphthae, and some forms of peripheral spondyloarthritis). The course of inflammatory bowel diseases in children is more severe than in adults. Extraintestinal manifestations may precede intestinal ones by months or years and may lead to false diagnoses and delayed treatment. Patients with extraintestinal manifestations often first consult other specialists, such as ophthalmologists, orthopaedic surgeons, or rheumatologists, before being diagnosed with a gastroenterological disorder. Ankylosing spondylitis or primary sclerosing cholangitis, which co-occur in patients with ulcerative colitis pose a greater health problem for some patients than the main intestinal disease (Table 1) [1–6].

Gastrointestinal complications are as follows:

- a. Toxic megacolon (megacolon toxicum): a potentially lethal complication was observed in 3–4% of all patients with ulcerative colitis. Toxic megacolon usually occurs in patients whose whole area of the large intestine (pancolitis) has been affected shortly after the onset of the disease. Pathophysiological factors include inflammation-induced severe damage to the intestinal wall, electrolyte imbalance, and hypoproteinemia. Antidiarrheals and a barium enema may additionally contribute to the development of the complication. The removed intestine is characterised by significant thinning, fragility of the walls, and segmental mucosal atrophy. Histopathological examination shows significant hyperaemia, infiltration of all layers of the intestinal walls, and multiple small microperforations. Diagnostic criteria for megacolon toxicum involve radiological symptoms of large bowel distension, clinical symptoms (fever, HR >120/min and leukocytosis), and at least one of the following symptoms—dehydration, impaired consciousness, and decreased RR. The physical examination reveals increased tension and tenderness of the abdominal wall to palpation, as well as absent or subdued peristaltic sounds. In some cases, peritoneal symptoms occur, which may indicate an intestinal perforation. The diagnosis of toxic megacolon is based on the clinical picture and X-ray picture of the abdomen, which will show extensive distension of the colon filled with gas. A radiological criterion for megacolon is the transverse colon exceeding 6 cm in diameter in the body’s midline. Laboratory tests show leukocytosis, anaemia, hypoalbuminaemia, and hypokalemia.

- b. Perforation of the large intestine may further complicate toxic megacolon but it may also occur independently in a severe course of the disease. It occurs in severe, often first flares of ulcerative colitis and most often affects the left half of the colon. The clinical presentation is dominated by the symptoms of acute abdomen and peritonitis. The presence of free gas trapped within the peritoneal cavity visible in the abdominal X-ray picture or CT scan is the most reliable confirmation of the perforation.
- c. Intestinal bleeding: caused by significant inflammatory lesions in the rectal and colonic mucosae. It is a life-threatening condition that can only be averted by colectomy.
- d. Intestinal stricture: observed in 12% of patients with UC after 5–25 years with the condition, typically in the sigmoid colon or the rectum. However, it may occur at any time during the course of the disease. A severe course of the disease gradually leads to fibrosis and strictures in the lumen of the intestines. It is caused by the hypertrophy and thickening of the muscularis mucosa with accompanying fibrotic lesions. Their length does not usually exceed 3 cm but may reach 20–30 cm. The diagnosis of this complication based on clinical symptoms is difficult. Symptoms of strictures involve constipation, abdominal distension, sometimes more severe diarrhoea, or faecal incontinence. In the endoscopic and radiological examination, the lesions may imitate those of colorectal cancer.
- e. Colorectal cancer: the most serious, if remote, consequence of ulcerative colitis is colorectal cancer. Risk factors include prolonged ulcerative colitis (over 8 years), large affected area of the large intestine, and the onset of the disease in childhood. An early diagnosis is difficult. Colonoscopy, together with multiple biopsies of all parts of the large intestine play the greatest role in diagnostics. These examinations also contribute to the detection of the characteristic precancerous lesions in the form of intestinal epithelial dysplasia. Low- or high-grade dysplasia is observed in flat, macroscopically insignificantly changed, or normal mucosa or in small irregularities or polypoid elevations in the mucosa, endoscopically detectable.
- f. Perirectal lesions occur in 5–18% of patients with ulcerative colitis. They include thrombosed or prolapsed haemorrhoids, skin maceration, fissures, abscesses, and/or perianal fistulas. The majority of these lesions are secondary to diarrhoea and are characterised as acute bacterial complications. The diagnosis is based on a thorough physical examination. The main type of the internal fistula in IBD is rectovaginal fistula.
- g. Gastrointestinal amyloidosis is characterised by the depositing of protein substances (amyloid) in the gastrointestinal wall leading to its thickening and disorders of the motor activity of the gastrointestinal tract [1–6] (**Table 2**).

Extraintestinal symptoms. Many patients with ulcerative colitis experience symptoms from other organs and systems. Comorbidities, also referred to as systemic complications can be divided into two groups—conditions that occur mainly in the exacerbation of colitis ulcerosa (e.g., arthritis of the large joints, iritis, and erythema nodosum) and conditions occurring independently from the activity of colitis (e.g., ankylosing and most complications from the liver and bile ducts).

Intestinal complications of ulcerative colitis	Frequency of occurrence
Megacolon toxicum	3–4%
Perforation	2.5–3.5%
Haemorrhage	
Perirectal lesions	5–18%
<ul style="list-style-type: none">• fissures• abscesses• fistulas• Haemorrhoids/prolapsed haemorrhoids	
Inflammatory polyposis	10–12%
Stricture	8–12%
Cancer	0.5–1.5%

Table 2.
Intestinal complications of ulcerative colitis.

2. Malnutrition

Malnutrition is a significant complication in children with inflammatory bowel disease that results in delayed growth and puberty. Fatigue and loss of appetite are sometimes also observed. They may imitate anorexia nervosa.

Inhibition of growth and/or puberty. The main causes include chronic inflammation, abnormal level of nutrition, and intake of glucocorticoids for medicinal purposes [2, 4, 5].

3. Hepatic lesions

Liver-related symptoms may present as hypertransaminasemia caused by the disease or as a result of the treatment (sulfasalazine, steroids, azathioprine, and parenteral nutrition). Other serious complications include autoimmune hepatitis and primary sclerosing cholangitis. Liver-related symptoms are observed in about 50% of patients with ulcerative colitis. *Primary sclerosing cholangitis (PSC)*. A total of 90% of patients with primary sclerosing cholangitis have ulcerative colitis. Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of complex aetiology that leads to damage to intra- and extrahepatic bile ducts. The following factors play a part in the etiopathogenesis—genetic (HLAA1, B8, DR3), autoimmune, infectious, and environmental (the impact of diet and the gastrointestinal microbiome). The disease is characterised by the narrowing of the bile ducts that impairs the flow of the bile and leads to cholestasis. Consequently, it may result in portal hypertension, cirrhosis/ liver failure, maldigestion, and malabsorption of fat and vitamins. Europe and North America report the highest incidence rate, at 4.1–16/100,000 of inhabitants. The highest incidence rate is among 20–40-year-olds. The incidence rate of PSC in the paediatric population is reported at 0.2/100,000/year, with a higher rate among the adult population, at 0.5–1/100,000/year.

The clinical manifestation is not characteristic. In 40–60%, there are no clinical symptoms, and the observed abnormal parameters of cholestasis and damage to the liver suggest primary sclerosing cholangitis.

In some patients, the skin and the sclera turn yellow, and other symptoms involve itching, fatigue, loss of body weight, weakness, epigastric pain, and/or episodes of fever. *PSC* is a progressive condition leading to cirrhosis and liver failure. A total of 50% of patients with primary sclerosing cholangitis require a liver transplant within 10–15 years of diagnosis. A total of 50–80% of patients with *PSC* have a co-existing inflammatory bowel disease (ulcerative colitis more often than Lesniowski-Crohn's disease). Lesions more often affect the right colon, with the rectum remaining unaffected (free). Interestingly, only 2–4% of patients with ulcerative colitis, and 1.4–3% of those with Lesniowski-Crohn's disease have co-existing *PSC*. Other autoimmune conditions often co-exist in patients with *PSC*. They are type 1 diabetes mellitus, coeliac disease, autoimmune pancreatitis and Hashimoto thyroiditis, glomerulonephritis, and/or arthritis. *Diagnosis*. Laboratory tests reveal elevated parameters of cholestasis and damage to the liver. A total of 40–50% of patients have increased IgM and IgG, and in 20–50%, there are anti-nuclear antibodies and/or anti-smooth muscle antibodies. In 50–70% of patients, pANCA antibodies are present. Cholangio-MRI reveals the characteristic picture of strictures with subsequent dilatations of the intra- and/or extrahepatic bile ducts. Retrograde cholangiopancreatography (ERCP) is performed in the case of clinical uncertainty, or a need for treatment (sphincterotomy, stenting) and/or for cytology to confirm or exclude cholangiocarcinoma. Similarly, histopathological assessment of liver biopsies is only conducted in the case of diagnostic uncertainty. Histopathological examination reveals fibrosis around bile ducts—“onion skin” in 20–40%, inflammatory infiltrate in portal areas, the proliferation of the bile ducts, and subsequent biliary ductopenia. *Complications*. Inflammation and fibrosis lead to the development of cirrhosis of the liver. Patients with *PSC* are at a higher risk of developing cholangiocarcinoma and/or hepatocellular carcinoma. Primary sclerosing cholangitis is linked with an increased risk of colorectal cancer (in 9% after 10 years of diagnosis, in 31% after 20 years, and in 50% after 25 years), cholangiocarcinoma, and/or gallbladder cancer (400× greater risk). Close to 50% of gallbladder polyps in patients with *PSC* is malignant. 1/3 of cholangiocarcinoma in adults is diagnosed at the same time as *PSC*. The treatment of primary sclerosing cholangitis involves ursodeoxycholic acid, which, despite being controversial, reduces the risk of dysplasia within the large intestine. It is possible that ursodeoxycholic acid lowers the concentration of endogenic, harmful metabolites of bile acids. There has been research on the inclusion of vancomycin in the treatment of patients with *PSC*, but its efficacy was not proven. In the case of strictures in bile ducts and cholelithiasis, the procedure of ERCP is adopted. A liver transplant is necessary in the case of recurrent cholangitis, end-stage liver failure, portal hypertension, and/or treatment-resistant pruritus. *Autoimmune hepatitis*. In some patients, it accompanies primary sclerosing cholangitis. The clinical manifestations are not characteristic—sometimes weakness, the yellowing of the skin and the sclera, pruritis and hepatosplenomegaly. Laboratory tests reveal elevated parameters of liver damage and cholestasis, hypergammaglobulinemia, and high levels of IgG. Histopathological assessment of a liver biopsy is crucial for the final diagnosis. The treatment involves immunosuppressive drugs (glucocorticoids, azathioprine, and cyclosporine). *Cholelithiasis*. Cholelithiasis is more frequently observed in patients with Lesniowski-Crohn disease than in those with ulcerative colitis, especially with the lesions affecting the ileum terminale and after ileocecal resection (link with interrupted enterohepatic circulation). In patients with ulcerative colitis, cholelithiasis occurs noticeably and frequently following large bowel resection and is linked to the abnormal absorption and transport of bile acids. The problem may affect even 10–30% of patients. *Liver steatosis* is the most frequently

observed liver pathology in the course of inflammatory bowel disease. The aetiology highlights the role of an unhealthy diet, loss of body weight, and steroid therapy. Hepatic steatosis may affect even 40% of patients with ulcerative colitis. Hepatic steatosis often correlates with the severity of the inflammatory bowel disease and often subsides once treated. *Hepatic amyloidosis*—the problem concerns 0.07% of patients with ulcerative colitis. The aggregation of amyloid in the liver leads to asymptomatic hepatomegaly. No correlation has been shown between the occurrence of amyloidosis and the advancement of intestinal lesions, the scope and duration. *Liver abscess*. It occurs more often in the course of Lesniowski-Crohn disease. Laboratory tests show leukocytosis and elevated activity of alkaline phosphatase. Liver abscesses may develop as a result of direct contact with an abdominal abscess or the hematogenous spread of inflammation. *Drug-induced hepatotoxicity*:

- 5-ASA-elevated aminotransferases
- Azathioprine/6-mercaptopurine—asymptomatic elevated aminotransferases (in 5%), vein thrombosis
- Methotrexate—steatosis, fibrosis, and cirrhosis of the liver, depending on the dose [7–16].

4. Pancreatic complications

Pancreatitis. Increased activity of amylase/lipase in the blood serum is observed in 14% of patients with inflammatory bowel disease. It is most often asymptomatic and has no link with the activity of bowel disease. *Acute pancreatitis* may be a side-effect of treatment with the following drugs—azathioprine, sulfasalazine, and mesalazine. The symptoms usually occur within the first weeks of treatment. The course of the disease is usually mild and rapidly subsides once the triggering factor has been withdrawn. Apart from the impact of the applied treatment, the pathomechanism has not been entirely determined. It may be connected with autoimmune factors and the formation of antibodies. *Autoimmune pancreatitis*. The impact of inflammatory mediators and the presence of anti-pancreatic antibodies has been considered. It is very rarely observed in the paediatric population [1–6, 17, 18].

5. Skin lesions

Skin lesions are observed in about 3–10% of patients with ulcerative colitis. *Erythema nodosum* is an inflammatory condition that affects the subcutaneous fat in the skin and is characterised by the formation in the subcutaneous tissue of weakly delineated, flatly elevated, tender, red and warm nodules of 1–1.5 cm in diameter (the nodules may merge). They usually appear on both sides of the lower leg (less commonly on the calves), but they are not uncommon on the thighs, buttocks, arms, and torso. The nodules do not fade after 2–9 weeks, they subside without leaving scars, and they may leave post-inflammatory discolouration. It usually precedes a relapse of the intestinal condition and related gastrointestinal manifestations. However, in some patients, the course of this skin complication is independent of the activity of ulcerative colitis. It may affect even 10–15% of patients with ulcerative colitis, more

of whom are women. The treatment involves the treatment of the intestinal disease, and glucocorticoids also render good results. *Pyoderma gangrenosum*. It occurs very rarely in the paediatric population with inflammatory bowel disease, affecting less than 1% of patients. Pyoderma gangrenosum most often presents in its severe, classic form (skin ulcers) or milder, pustular form. The lesions rapidly transform into ulcers affecting the skin and the superficial layer of the subcutaneous tissue. They are mainly located within the pretibial region, but they may affect every body part. They may lead to abscesses, ulcers, and osteomyelitis. Pyoderma gangrenosum does not always correlate with the activity of intestinal disease. Histopathological examination shows necrotic lesions in the skin, substantial leukocyte infiltrations, thrombosed veins, and petechiae. The healing process is difficult and leaves behind anthropic scars. The treatment involves high doses of glucocorticoids and in some cases cyclosporine and infliximab. *Sweet's syndrome* is a form of erythema exsudativum multiforme with accompanying fever and neutrophilia, also seen in patients with ulcerative colitis. Lesions may resemble erythema nodosum but steroid treatment rapidly brings improvement. *Psoriasis*. Occurs five times more frequently in patients with ulcerative colitis than in the population. It may be a side effect of the applied biological treatment. *Epidermolysis bullosa acquisita*. Following a mechanical injury, large subepithelial blisters form, often blood-filled. The lesions are most often located on the hands, the soles of the feet, in the elbow creases and behind the knees. Erosions within the oral cavity are observed in some patients. *Necrotizing vasculitis*. May lead to peripheral gangrenous lesions.

Stomatitis aphthosa occurs in around 3% of patients with ulcerative colitis. Mouth ulcers most often present as small and rather shallow erosions in the mucosal surfaces of the cheeks, soft palate, and/or the tongue. Such ulcers require differential diagnosis with moniliasis, which is another complication following severe lapses of ulcerative colitis treated with glucocorticoids and antibiotics [19, 20].

6. Rheumatoid symptoms

Arthritis may affect single or many joints, including knees, elbows, and/or hips (around 3.8%). Ankylosing spondylitis and sacroiliitis may also occur. Manifestations from the musculoskeletal system are the most common extraintestinal symptoms of inflammatory bowel disease, with as many as 25% of patients with UC affected. Arthritis may occur together with, or irrespective of the level of activity of inflammatory bowel disease. Lesions of the joints occur more often in patients with intestinal and extraintestinal complications, such as abscesses, pseudopolyps, perirectal lesions, and/or lesions in the mouth, erythema nodosum or pyoderma gangrenosum. The location of arthritis may change and may move from one joint to another. It usually lasts several weeks, rarely leading to joint deformity, and subsides following standard treatment for IBD. Patients are diagnosed with arthralgia (the presence of pain not linked with the inflammation) and spondyloarthropathies (arthritis with swelling, pain, redness, impaired mobility, and lesions seen in the imaging tests). The pathophysiology of these conditions is not fully known. *Classification*: A. Type I arthritis—type I arthropathy—axial type—typically affects several large peripheral joints (usually fewer than five), with often nonsymmetric and self-limiting lesions, and linked with the activity of the primary condition. It may precede the intestinal symptoms. It does not lead to the destruction of the affected joints. B. Type II arthritis—type II arthropathy—peripheral type—concerns at least five small peripheral

joints, symmetric and with no link to the primary condition. Lesions occurring in this type are usually chronic and recurring. Synovitis occurs in both types. Synovial biopsies indicate non-characteristic lesions in the form of increased blood flow, endothelial proliferation, and mononuclear cell infiltration. Laboratory tests in arthritis are not specific. Leukocytosis, the ESR, and C-reactive protein correlate more with the activity of the intestinal disease and are of little value in the diagnostics of lesions in the joints. Synovial fluid analysis shows an increased count of leukocytes with the majority of neutrophils. Radiological analysis of peripheral joints shows mild oedema of the tissue, osteoporosis, periostitis, and exudation, usually without erosions or bone destruction. CT and/or MRI scans prove very useful for the assessment of lesions within the sacroiliac joints. Axial spondyloarthritis is treated with relevant physiotherapy, rest, and specialist medication (sulfasalazine and mesalazine, among others)—as the only treatment of the primary condition, which, once in remission will also result in the withdrawal of the manifestations from the musculoskeletal system. Lesions in type II inflammation are often chronic and recurring, with both rheumatological and physiotherapy assistance necessary.

Ankylosing spondylitis occurs in 4–8% of patients with IBD. Men are affected more often than women. In around 60% of patients, the HLA-B27 antigen is present. The occurrence of ankylosing spondylitis is over 30 times higher in patients with ulcerative colitis compared to the general population. No correlation between the advancement of lesions in the joints and that of the lesion of the large intestine has been shown. The clinical manifestations of AS involve pain and stiffness in the lumbar spine, in particular in the morning or after a period of rest. The disease is progressing and is characterised by periods of relapse. It may lead to significant impairment of mobility. First-line treatment involves physiotherapy and in some cases immunosuppressants. *Sacroiliitis* occurs in around 14% of patients with inflammatory bowel disease but is mildly symptomatic in 90% of cases. There is no link between sacroiliitis and the activity of intestinal disease. The course is often asymptomatic, and the condition is diagnosed incidentally during radiological tests. The treatment involves sulfasalazine, analgesics, and physiotherapy. *Fibromyalgia syndrome* affects soft tissues, and its clinical manifestations are typical of the area affected. The most frequent symptoms are muscular pain and pain in the areas of tendon insertion points, for example, within the shoulder girdle, elbow joints, pelvis, knee joints, and rib attachments. In the physical examination, tenderness of the tendon insertion points is noticeable (tender points). The treatment involves anti-inflammatory and analgesic medication, as well as regular physiotherapy [1–6, 21–24].

7. Ophthalmological manifestations (1%)

Ophthalmological manifestations concern mainly patients with ulcerative colitis, with the whole area of the large intestine affected and accompanying lesions in the joints. They occur in 6–60% of patients with IBD, almost twice as frequently in men as in women. These complications are typically one-sided, and their presence is linked with the activity of the primary condition. The most common ones involve watering eyes, burning eyes, pain in the eyes, light sensitivity, conjunctival hyperaemia, scleral hyperaemia, impaired visual acuity, or complete vision loss. Ophthalmological complications may also be asymptomatic. Inflammation may develop in any part of the eye. Episcleritis, together with uveitis is the most common ophthalmological complication of inflammatory bowel disease. Less frequent conditions include iritis

scleritis, keratitis, and conjunctivitis. Among complications related to the treatment of IBD, cataract is often observed, which is probably linked to the prolonged use of glucocorticoids.

Iritis. It presents with blurred vision, headache and pain in the eye, photophobia, and irritated conjunctiva. *Uveitis*. Its course is often insidious and chronic. The clinical manifestations involve painful eyes, blurred vision, photophobia, and/or headaches. This disease occurs four times more frequently in women. In the physical examination, inflammatory lesions are concluded in the front area of the uvea, corneal opacity, and/or conjunctivitis. Lesions are usually both-sided. In 75% of patients arthritis also occurs. The treatment involves glucocorticoids, used topically and systemically. *Episcleritis*. Its course may be asymptomatic (2–5%) or may present as burning and sore eyes. The physical examination shows vascular injection of the ciliary body and visible inflammation in the episclera. The treatment involves treating the primary disease and topical steroids. *Cataract*. May be linked with the use of glucocorticoids.

Rare ophthalmological complications are as follows:

- Central retinal vein occlusion and retinal vasculitis.
- Subepithelial keratopathy.
- Peripheral corneal ulcer and/or corneal infiltrates.
- Central serous chorioretinopathy [1–6].

8. Haematological complications

Anaemia concerns almost 30% of patients with IBD. It significantly affects the quality of life. Chronic blood loss, impaired absorption, and the impact of cytokines play an important role. Similarly, the applied treatment, involving sulfasalazine, methotrexate, and azathioprine also contributes to the condition. In the treatment of anaemia linked to ulcerative colitis, an early therapeutic intervention that is suited to the deficiencies and activity of the intestinal disease is extremely important.

Hypochromic anaemia is caused by microhaemorrhages within the gastrointestinal tract and ongoing inflammation. Anaemia caused by B12/folic acid deficiency includes autoimmune haemolytic anaemia and thrombocytopenia/thrombocytosis [1–6, 25–27].

9. Osteoporosis/osteopenia

Reduced bone mineral density has a complex mechanism and is related to deficiencies in protein and calories, abnormal absorption of calcium, vitamin D deficiency, glucocorticoid therapy, and the adverse impact of proinflammatory cytokines (TNF- α , IL-1 α , IL-1 β , and IL-6) on the bone tissue metabolism. Osteoporosis occurs in approximately 15% of patients with inflammatory bowel disease. Osteoporosis and osteopenia develop particularly often in patients with co-existing sclerosing cholangitis, probably as a result of the abnormal transportation and absorption of bile acids. It has been shown that patients with IBD statistically significantly more often experience fractures of long bones and the corpus vertebrae.

Densitometry is a screening test and should be performed in particular in groups of patients with severe IBD, especially treated with glucocorticoids [1–6].

10. Nephrological complications

In patients, especially in paediatric ones, the calcium obtained from food interacts with unabsorbed fatty acids. This leads to an increase in urine oxalate excretion, and significantly increases the risk of urolithiasis. Some studies concerning IBD mention cases of glomerulonephritis caused by concentrations of immune complexes in patients affected. Recurring urinary tract infections, hydronephrosis, and renal amyloidosis are reported relatively more frequently compared to the general population.

Urolithiasis. Occurs particularly often in patients with Lesniowski-Crohn disease and with the affected small intestine or following its resection. It develops as a result of calcium-binding with unabsorbed fatty acids.

Interstitial nephritis. Also known as tubulointerstitial nephritis is an inflammation process that develops mainly in the areas of the kidney other than the glomeruli. Those areas, that is, the renal interstitium and renal tubules become infiltrated with inflammatory cells, which leads to abnormal renal functions. The symptoms of acute interstitial nephritis may occur from the 1st day to over 2 months (on average within 3 weeks) after the triggering factor (e.g., the intake of new medication). The most common manifestations include fever and pain within the lumbar area. Chronic interstitial nephritis may be asymptomatic for many years. *Glomerulonephritis* is a group of diseases characterised by the inflammation of the glomeruli, which impairs normal kidney functions. Inflammatory cells (lymphocytes and leukocytes) and antibodies concentrate within the glomeruli that trigger the hyperplasia of the normal glomerular cells. If the inflammation is chronic, the glomeruli become fibrotic over time, and this leads to renal failure. *Infections of the urinary tract.* Frequently recurring cystitis; E.coli being the most frequently isolated pathogen. *Hydronephrosis* is caused by the obturation of the ureter by inflammatory lesions within the abdominal cavity. Renal amyloidosis [1–6, 28–30].

11. Cardiological complications

Pericarditis, including drug-induced; sulfasalazine/mesalazine [1–6, 31, 32]. Myocarditis occurs in patients with ulcerative colitis twice as frequently as in the healthy population.

12. Pulmonary complications

The following occur with a greater frequency—pulmonary vasculitis, chronic bronchitis and bronchiolitis, and bronchiectasis (more extensive and more rapidly developing compared to those of another aetiology). It is sometimes difficult to determine whether the pulmonary lesions are an extraintestinal manifestation or independent comorbidity. *Interstitial pneumonia.* Interstitial lung diseases are characterised by progressive damage to the architecture of the alveoli and the lungs, which leads to the loss of normal pulmonary functions.

Drug-induced pulmonary complications are as follows:

- Eosinophilic pneumonia/pleuritis: The clinical presentation is dominated by fever, cough, dyspnoea, and respiratory distress. The HRCT test shows ground-glass areas and the BAL fluid eosinophil greater than 25%.
- Methotrexate-related complications—after as little as 1 dose and up to 4 weeks following the last dose; folic acid does not protect from such complications. Imaging tests show diffuse lesions, interstitial infiltrates, fibrosis, and granulomas.
- Azathioprine-related complications—rarely-interstitial pneumonia; discontinuation of the medication usually leads to improvement and the withdrawal of the symptoms.
- Anti-TNF α -related complications-usually interstitial pneumonia-often in older patients, with previous lung strains and with simultaneous immunosuppressing therapy-discontinuation of treatment leads to the withdrawal of the symptoms in most patients.

Opportunistic infections. Infections with *Mycobacterium tuberculosis*, *Pneumocystis carini*, *Listeria monocytogenes*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, and Cytomegalovirus.

The pulmonary lesions are usually either asymptomatic or oligosymptomatic. Pulmonary function tests show abnormalities in over 40% of patients. The classic thoracic X-ray in the majority of patients is non-characteristic. A High-resolution CT scan, on the other, is a helpful diagnostic tool.

Also, patients with inflammatory bowel disease develop asthma more often [1–4, 33, 34].

13. Arterial/vein thrombosis

Occurs 3–4 times more often in patients with inflammatory bowel disease compared with the healthy population. The frequency of occurrence increases with age and concerns 2–10% of patients with IBD. Vein thrombosis is the dominant condition. The treatment involves low molecular weight heparin.

Types of thrombosis are as follows:

- deep vein thrombosis.
- pulmonary embolism.
- thromboembolic lesions of intracranial vessels and/or of the eye.

The significance of these complications are mainly due to the young age of the affected patients, a large percentage of deaths and complex treatment (the use of anticoagulants in patients with gastrointestinal bleeding). It is often recurring. Vein thrombosis in the course of IBD is characterised by the atypical location of the thrombotic lesions, correlates with the activity of the intestinal disease and has a proven link with the use of glucocorticoids. Active intestinal disease with thrombocythaemia and increased activity of blood coagulation factors, as well as an increase in the concentration of homocysteine, are additional factors contributing to the development of

thrombosis. Thromboprophylaxis should be adopted in patients with medium/acute exacerbation of inflammatory bowel disease [27].

14. Neurological complications

- Peripheral neuropathy
- Myelopathy
- Myasthenia

Vascular lesions in the central nervous system occur equally frequently in patients with ulcerative colitis and those with Crohn's Disease. They usually develop 5–6 years following the onset of the intestinal disease and often coincide with other extraintestinal manifestations of IBD [1–6, 35, 36].

15. Summary

- Better awareness of the initial symptoms, the course of the disease and extraintestinal manifestations, often preceding IBD may shorten the period from the onset of the symptoms to the diagnosis.
- Arthritis of the large joints, iritis, and erythema nodosum occurs mainly during the periods of the exacerbation of ulcerative colitis.
- Ankylosing spondylitis and most complications in the liver and bile ducts happen independently from the activity of the intestinal disease.
- Extraintestinal manifestations require differential diagnosis with conditions occurring independently from IBD and drug toxicity.

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