Extraintestinal manifestations of Crohn's disease

Bartosz Wójcik[1], Karolina Loga[1], Marcin Włodarczyk[2], Aleksandra Sobolewska-Włodarczyk[1,2], Milena Padysz[1], Maria Wiśniewska-Jarosińska[1]

[1]Department of Gastroenterology, Medical University of Lodz, Lodz, Poland
[2]Department of Biochemistry, Medical University of Lodz, Lodz, Poland

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Adress for correspondence: Marcin Włodarczyk, Department of Biochemistry, Medical University of Lodz, 6/8 Mazowiecka St, 92-215 Lodz, Poland, phone: +48 42 272 57 07, fax: +48 42 272 56 94, e-mail: dr.mwlodarczyk@gmail.com

Crohn's disease (CD) belongs to a group of inflammatory bowel diseases (IBD) and is characterised by chronic, segmental, granulomatous inflammation with periods of exacerbation and remission, which may involve any part of the gastrointestinal tract. Crohn's disease is diagnosed mainly in young adults, with a peak occurrence between ages 15 and 30 years. The precise pathogenesis is still not entirely identified and understood. Crohn's disease symptomatology is non-specific and very diverse. General symptoms such as fever, weakness, and weight loss are accompanied by intestinal symptoms associated with chronic inflammation of the intestinal mucosa, such as abdominal pain and chronic diarrhoea [1, 2]. Occasionally, extraintestinal manifestations (EIMs) may occur, with a prevalence varying from 6% to 36%. The most common EIMs involve joints, skin, uvea, blood, and the hepatobiliary system. Arthropathy associated with IBD is definitely the most common EIM, clinically divided into peripheral and axial involvement. The most diverse are cutaneous manifestations, in which specific granulomatous skin lesions, non-characteristic reactive lesions, skin symptoms secondary to nutritional malabsorption, and iatrogenic skin changes are distinguished [3]. Unclear pathogenesis of EIMs in patients with CD makes treatment strategies difficult and requires a multidisciplinary approach. The aim of this work was to report a case of a CD patient with a variety of severe extraintestinal symptoms that appeared during exacerbations and undertaken treatment of the disease.

A 26-year-old female patient with a 6-year history of CD presented multiple extraintestinal manifestations that developed one year before diagnosis of the basic disease. The first symptoms appeared during pregnancy in January 2006. She complained of abdominal pain, chronic diarrhoea, and hypertrophy of labia minor and major. In October 2006, because of severe intestinal and vulvar symptoms a caesarean section was performed. In the postnatal period the patient presented a high fever and further intestinal aggravation with hemodiarrhea. The vulva underwent further growth restricting the free movement of the patient. Within one year of frequent dermatological, endocrinological, and immunological consultations, and HPV tests the correct diagnosis was not established. In December 2007, due to the appearance of perianal lesions the patient was admitted to the Department of Gastroenterology, Medical University of Lodz and referred for endoscopic examination. Colonoscopy with histological confirmation was crucial for the diagnosis of CD. Pharmacotherapy with azathioprine (AZA), mesalazine (MSZ), methylprednisolone (MP), and supplementation of folic acid (FA) was administered with a partial clinical response, but no healing of any of the EIMs. In February 2008, due to lack of response to undertaken treatment, the patient was qualified for biological therapy with certolizumab (Cimzia) in a clinical trial: No. C87085/C87088. In the first weeks of therapy clinical improvement was obtained, a reduction in diarrhoea was observed, lower incidence of fever, and less severe abdominal pain. However, perianal lesions and vulva size reduction was not observed. From February 2008 to August 2008, during biological therapy, the patient was hospitalised three times because of the severity of persistent constipations. In September 2008 she was admitted to the hospital with symptoms of CD exacerbation. The patient presented severe pain in the lower abdomen and lower right-side pelvic area, gas bloating, loose stools, and fever. One-week pharmacotherapy with MP, AZA, and MSZ resulted in clinical improvement, followed by another dose of certolizumab administration. In April 2009 the symptoms of CD exacerbation appeared again with significant increase of body temperature up to 40°C. Additionally, symptoms were accompanied by non-itchy psoriatic-erythema skin

lesions involving the whole body. In the scalp region, lesions of alopecia areata (AA) were observed and confirmed by histopathology examination. Monotherapy with topical corticosteroids, within 2 months, had satisfactory clinical response with total regression of skin lesions without leaving scars. The patient also reported severe lower back pain caused by co-existing sacroiliitis (SI). During the 3-week hospitalisation the patient underwent rehabilitation, treatment with non-steroidal anti-inflammatory drugs (NSAIDs), and broad-spectrum antibiotic therapy; however, the immunomodulatory therapy with AZA and certolizumab was continued. In August 2010 the patient was admitted to the Department of Gastroenterology and Transplantology, Clinical Hospital MSWiA in Warsaw with intestinal symptoms of CD exacerbation and exfoliative pus-producing lesions of the vulva and perineum regions. Magnetic resonance imaging of the pelvis minor was performed showing a monstrously enlarged labia minor and slightly less enlarged labia major, suggesting inflammation or venous stasis. Oedema of perineal soft tissue around urethra, vaginal vestibule, and anus was also revealed. The examination visualized intersphincteric abscesses, perianal fistula, and inflammatory tumour with abscess in the mesentery of the small intestine involving the distal part of the ileum and caecum. The performed colonoscopy showed inflammatory lesions mainly in the distal part of the small intestine. Advanced intestinal lesions and patient qualification for surgery led to termination of the biological therapy. Performed surgery in September 2010 involved segmental resection of the distal ileum and caecum, with diverting loop ileostomy. In the postoperative period, the intestinal symptoms of CD, such as abdominal pain, nausea, and chronic diarrhoea, subsided, but a disorder of wound healing with abundant leakage of serous-bloody content occurred. The histopathological examination of tissue samples from the perineal lesions showed inflammatory infiltration in the dermis around the hair follicles and apocrine glands with their destruction and creation of granulation tissue resorption. In the stroma, the collagenisation processes associated with chronic inflammatory infiltration was observed. In November 2010 due to unsatisfactory clinical and intestinal response the patient was qualified for annual treatment with infliximab. In March 2011 the patient underwent vulvoplasty, which consisted of labia major and minor simple bilateral partial resection. The histopathological examination of excised hypertrophic labia showed angiomyofibromatosis type lesions. In August 2011, during the infliximab therapy, a high fever and new additional cutaneous manifestations were observed. The histopathological results of specimens from the skin eruptions confirmed the diagnosis of drug-induced psoriasis and AA. In November 2011 the last dose of infliximab was administered. Spontaneous total regression of psoriasis and AA was noted within the following 2 months. In January 2012 the patient underwent surgical restoration of the gastrointestinal track continuity. In the postoperative period, impaired wound healing with formation of serous fluid was observed. Skin sutures were removed leaving the wound open to heal by granulation. Due to the complicated postoperative period and weakness of the abdominal wall ventral hernia occurred. At present, the patient is in a period of clinical remission of CD, but due to low quality of life the patient requires further surgical procedures of hypertrophic vulva, perianal lesions, and abdominal hernia.

Recent studies on IBD pathogenesis have led to a general consensus among investigators that both CD and ulcerative colitis (UC) are the result of the combined effects of four main groups of factors: environmental, immunological, genetic, and infectious. However, none of them alone can be a trigger factor for the development of inflammatory process. In the reported case, one of the trigger factors was the chronic stress associated with early, unplanned pregnancy before the end of scheduled education. Intensive stress induces disturbances in the hypothalamic-pituitary-adrenal system. Neuroendocrine factors (e.g. corticotrophin-releasing factor and catecholamine), produced by the autonomic nervous system, erode the physiological barrier of the intestinal mucosa. Increased permeability allows the passage of various antigens, pathogens, and physiological flora to the intestinal wall, which can lead to excessive immune response [4]. Immunoregulatory disorders in CD patients are associated with simultaneous stimulation of many pathways with a predominance of Th1 response and incorrect activation of Th-17 dependent on IL-23 [5]. The occurrence of IBD depends on a combination of all above factors, which may explain why each patient presents different clinical manifestations and diverse response to therapy. In the reported case, apart from general and intestinal symptoms, a variety of EIMs were observed, characterised by perianal lesions and significant hypertrophy of the labia. Chronic and recurrent granulomatous processes in the perianal and genital regions are referred to in the literature as anogenital granulomatosis (AGG). Anogenital granulomatosis mainly presents with ulcers, fissures, lymphoedema, and characteristic histopathology, in which non-necrotising granulomatous inflammation is the most specific for CD patients. That term was introduced in 2003 to unify all the other terms appearing in the world literature (chronic hypertrophic vulvitis, granulomatous vulvitis, chronic edema of vulva, etc.). Vulvar le-

sions are categorised as developing via direct extension or as metastatic CD. Direct extension involves contiguous inflammatory expansion from the intestine at the vulva, for example through fistulas [6]. In the absence of established bowel disease or separation from the intestinal lesions by healthy tissues, a metastatic form may be suspected. The appearance of AGG in 80% of cases is associated with long-standing intestinal CD. When the granulomatous process occurs first, the appearance of intestinal symptoms usually develops within four months to 2 years [7]. The proposed treatment received variable and sometimes unsatisfactory results characterised by rapid regression and frequent relapses after treatment discontinuation. Pharmacotherapy includes topical and oral corticosteroids, salicylates, antibiotics such as metronidazole and ciprofloxacin, immunosuppressant therapies such as azathioprine and cyclosporine, and biological therapy with anti-tumor necrosis factor (TNF)-α, such as infliximab and adalimumab [8]. In the reported case, each of the non-invasive therapies were ineffective and vulvoplasty was performed. Another EIM reported by the described patient was severe low back pain with arthritis. According to European Spondyloarthropathy Study Group (ESSG) criteria, the presence of peripheral arthritis and/or axial inflammatory complaints in IBD patients and the absence of a rheumatoid factor is classified as spondyloarthropathy (SpA). In the reported case SI was diagnosed, which belongs to axial arthropathy. It is manifested by morning stiffness and pain in the back or buttocks. However, it can also be asymptomatic. Radiographic SI was confirmed in 10–32% of patients with IBD, which is presently considered to be the most frequent EIM of IBD. Differential diagnosis of SI in CD patients should consider ankylosing spondylitis (AS), another axial arthropathy that might be associated with IBD. It has been shown that in CD patients the antigen HLA-B27 is an independent risk factor for AS [9]. Chronic axial symptoms can become predominant in CD remission and may be indistinguishable from classical AS. During CD intestinal exacerbation of joint symptoms may be underestimated because low back pain can be attributed to bowel disease. The determination of human cartilage glycoprotein 39 concentrations in serum (a protein correlating with arthritis recurrence) may be useful in differential diagnosis of osteoarticular disorder and intestinal symptoms [10]. Non-steroidal anti-inflammatory drugs are the first-line drug treatment for axial arthropathy, with good clinical response in most cases. In IBD patients with arthritis a selective COX-2 inhibitor could also be administrated [2].

In the last decade the use of biological agents against TNF-α (anti-TNF-α) has had a significant impact on the effectiveness of CD treatment. The presented patient used two drugs from the group of anti-TNF-α: certolizumab and infliximab. Tumour necrosis factor α is a cytokine that takes an important role in the pathogenesis of CD. Biological therapies increased the number of achieved remissions, allowed for long-term maintenance and reduced symptoms during follow-up [11]. Anti-TNF-α introduced in order to obtain remission of CD may induce de novo psoriasis or exacerbate existing skin lesions. In the reported case, after months of certolizumab therapy the patient manifested generalised psoriatic lesions. The best known hypothesis that explains the psoriasis formation as a result of anti-TNF-α therapy suggests that a reduction of circulating TNF-α increases production of interferon-α (IFN-α) by Langerhans cells. A high level of IFN-α induces migration of T-cells in the dermis, leading to the development of psoriatic lesions [12]. Psoriasis induced by anti-TNF-α drugs is more common in women (58–68%), which was confirmed in the presented patient. The prevalence of psoriasis during anti-TNF-α therapy in various clinical settings was estimated at 0.6–5.3% and in IBD at 1.6–2.0% [13]. It is suggested that, despite the occurrence of psoriatic lesions during the biological therapy, it should be continued. Skin lesions are usually temporary and in many cases subside spontaneously. Studies confirmed that the majority of patients show a good response to topical therapy. Monotherapy with topical corticosteroids or in combination with other topical drugs (keratolytics, vitamin D analogues) or phototherapy (narrow band UVB or soak PUVA) is the most appropriate initial approach and should provide the expected clinical effect. If psoriasis is not self-limiting or does not respond to topical initial treatment, covers more than 5% of the skin surface, or in cases of pustular psoriasis, biological therapy should be discontinued and at the same time local or systemic treatment for psoriasis should be provided (methotrexate, retinoids, and cyclosporine) [14].

Another EIM of CD, which appeared in the reported case during the biological therapy with infliximab, was AA. The incidence of this disease is determined to within 1% and 1.7% of the population. In the literature it was noted that an AA can coexist with CD, but the pathogenesis of these relationships is unknown. The coincidence of these lesions may indicate that histopathological examination of specimens from the CD intestinal lesions and the AA lesions show a similar inflammatory infiltration composed of Th1-cells. In the last decade a number of papers were published describing the occurrence of AA during anti-TNF-α therapy with infliximab, adalimumab, or etanercept [15]. The pathomechanism of AA induced by biological agents has not been elucidated. Studies have proven that both lesions could develop *de novo*, as well as blocking TNF-α pathway.

The differential diagnosis of AA is considering scalp psoriasis. AA lesions that develop in the course of IBD and its treatment respond poorly to conventional and biological therapy. There is increasing evidence of AA treatment with thiopurines, primarily AZA [16]. Farshi *et al.* reported a satisfactory hair regrowth in patients with AA after 6 months of treatment with AZA [17].

The pathogenesis of CD has not been definitively known and defined. The coexistence of several trigger factors mean that every patient has a different manifestation and severity of intestinal and extraintestinal symptoms. The multitude of pathomechanisms make the response to undertaken treatment, including therapy affecting the immune system, extremely diverse. Due to the coincidence of a number of disorders of the human biological systems, it seems necessary to create cooperation among gastroenterologists, gynaecologists, rheumatologists, and dermatologists in order for early diagnosis and appropriate therapy. Looking at CD patients from a wider perspective allows clinicians to provide effective induction and maintenance of the intestinal remission, with fewer side effects.

Conflict of interest

The authors declare no conflict of interest.

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