Skin changes in the course of inflammatory bowel disease

Karolina Kopeć, Alina Jankowska-Konsur, Joanna Maj

Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Poland
Head: Prof. Eugeniusz Baran MD, PhD

Post Dermatol Alergol 2012; XXIX, 1: 35–39

Abstract

Crohn's disease and ulcerative colitis are classified as chronic inflammatory bowel diseases (IBD), which not only affect the intestinal tract but also involve other organs, including skin and mucous membranes. More than half of patients with IBD suffer from parenteral symptoms. Skin lesions may be related to the underlying disease and its complications or may have a reactive character. Most common dermatoses coexisting with inflammatory bowel diseases are: pyoderma gangrenosum, erythema nodosum, Sweet's syndrome, polyarteritis nodosa, leukocytoclastic vasculitis, erythema multiforme, mucosal lesions and local complications (fistulae, fissures and abscesses). This paper presents a rich spectrum of dermatological conditions associated with IBD.

Key words: inflammatory bowel disease, skin lesions, cutaneous Crohn's disease, pyoderma gangrenosum.

Introduction

Chronic inflammatory bowel disease (IBD) includes two enteritis: ulcerative colitis (colitis ulcerosa – CU) and Crohn's disease (Leśniowski-Crohn's disease – LCD). The etiology of both remains unknown. Genetic, environmental, infectious and immunological factors leading to chronic intestine inflammation with erosions, ulcers and necrosis are believed to contribute to the development of the two diseases. Parenteral IBD symptoms occur in more than half of patients. Inflammatory bowel disease mostly leads to the development of articular changes (peripheral arthritis, axial arthritis), mucosal and skin lesions as well as to eye symptoms (conjunctivitis, iritis and uveitis) [1].

In the course of chronic inflammatory bowel disease, skin lesions are found in approximately 5-50% of patients [2-4]. Statistically, more skin symptoms occur in patients with LCD (15-20%) than in patients with CU (10%) [5, 6]. They may develop in the course of the primary disease, as a complication in the form of fistulae, fissures and abscesses, or less commonly, as a cutaneous or mucosal variety of the disease. Skin lesions may also be reactive. The most common reactive dermatological diseases occurring in the course of IBD are erythema nodosum and pyoderma gangrenosum (PG) [7-10]. Less frequently the coexistence of IBD and Sweet's syndrome [11], nodular arteritis, leukocytoclastic vasculitis or erythema multiforme has been reported. Casuistic publications report the coexistence of IBD with epidermolysis bullosa [12, 13]. In patients with IBD, skin lesions may also occur as a complication of the therapy.

Skin changes in the course of inflammatory bowel disease

Fistulae and fissures

Fistulae and fissures are a common complication of IBD. It is estimated that these lesions develop over a lifetime in 20-40% of patients [14, 15]. According to some reports, the risk of developing fistulas reach even 85% [16]. These complications are often observed in patients with LCD, but do not belong to a typical clinical presentation of ulcerative colitis [14-16].

Fistulae and fissures are a symptom of an ongoing "transmural" inflammatory process. In patients with LCD, internal fistulae are formed between the intestine and the adjacent organs (e.g. entero-intestinal, vesicointestinal fistulae) and may be asymptomatic. The external fistula develops between the bowel wall and the surface of the adjacent skin, around the stoma or in the perianal location. Mostly cutaneous and perianal fistulae are diagnosed. They are accompanied by pain and characterized by the presence of seeping discharge irritating the surrounding skin, and the development of abscesses.

Treatment of fistulas in the course of LCD is complicated and depends on the location, severity of symptoms, num-

Address for correspondence: Karolina Kopeć MD, Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, 1 Chałubinskiego, 50-368 Wroclaw, Poland, e-mail: karolinakopec@gmail.com

ber of branches of the fistula, the patient's nutritional status, their operational history and the presence or absence of changes in the perianal area. Therapy involves surgical management, treatment with antibiotics, steroids, immunomodulatory, immunosuppressive drugs (sulfasalazine, azathioprine, cyclosporine A, methotrexate, tacrolimus, mycophenolate mofetil) and biologics (infliximab) [14-17].

Changes in the oral cavity

Changes in the oral cavity occur in 4-20% of patients with LCD [18]. Aphthous stomatitis characterized by the presence of shallow, circular ulcers covered by fibrin with an erythematous halo is frequently observed. Other lesions in the oral mucosa characteristic of IBD are: small nodules appearing on the gums, linear ulcers, perleche, gingival hyperplasia, granulomatous inflammation of the lips (Miescher cheilitis), cobblestoning and pyostomatitis vegetans (hyperplastic suppurative inflammation of the mouth) manifested by white-yellowish pustules which burst, leaving erosions and ulcers [5, 19].

Miescher cheilitis (granulomatous inflammation of the lip, cheilitis granulomatosa) (Figure 1) is a rare inflammatory disease, which was described in 1945 by Miescher. It is characterized by a painless, diffuse, sometimes asymmetric edema of the lip. The etiology is unclear, however, many authors emphasize the coexistence of Miescher cheilitis with LCD. Ratzinger *et al*. have demonstrated the coexistence of this illness with LCD in 30% of patients. Therapy is based on clofazimine and corticosteroids. Infliximab appears to be a promising alternative [20-22].

Reactive skin lesions in the course of inflammatory bowel disease

Pyoderma gangrenosum

Pyoderma gangrenosum (Figure 2) is a rare, ulcerative skin disease associated with many systemic diseases, including IBD. It is characterized by massive infiltration, consisting of neutrophils and secondary vascular damage. The available literature suggests that the disease is more frequently associated with ulcerative colitis than with LCD [4, 23]. Diagnosis is usually based on exclusion and the clinical presentation. It is important to remember that PG-like ulcers may occur in cutaneous LCD. Laboratory tests may be useful in searching potential basic diseases. Histology is not specific [24]. The most important aspect of the therapy is the treatment of the basic disease. In addition, the corticosteroids, cyclosporine A, mycophenolate mofetil, tacrolimus or TNF-α antagonists if associated with (rheumatoid arthritis) RA or LCD have been used [25-27]. Local management involves elevation of the extremities, careful dressing, avoiding surgical treatment, topical medication containing corticosteroids, cyclosporine and tacrolimus [27, 28].

Sweet's syndrome

World literature also describes the coexistence of Sweet's syndrome (acute febrile neutrophilic dermatosis) and IBD (approximately 40 cases) [29]. It is a disease similar to PG in terms of both histology and the mechanism of the formation of skin lesions. However, the clinical pictures are significantly different. In the course of Sweet's syndrome, pruritic, erythematous, edematous-infiltrative lesions which are frequently associated with fever and leukocytosis are observed. In the treatment, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs are useful [9, 29, 30].

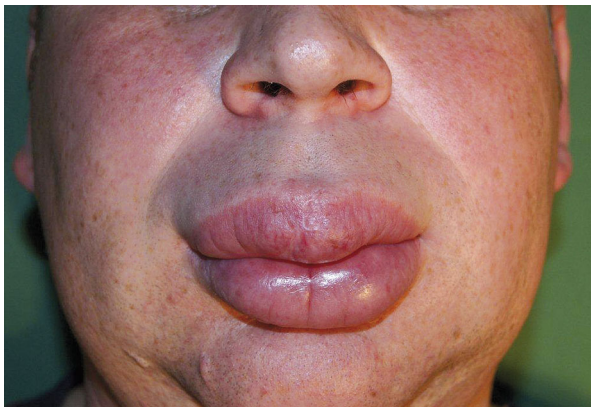

Figure 1. Miecher cheilitis

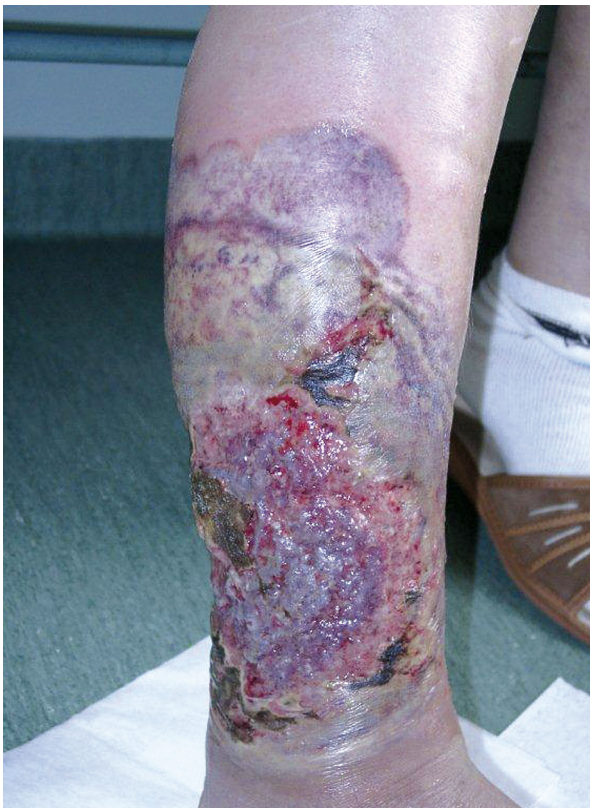

Figure 2. Pyoderma gangrenosum

Erythema nodosum

Erythema nodosum (Figure 3) occurs in about 4% of patients with IBD [31]. It is the most common form of subcutaneous tissue inflammation (panniculitis) characterized by deep, erythematous nodules, which usually symmetrically occupy the front surface of lower legs. Diagnosis is based on the clinical presentation and prognosis depends on the underlying disease [32]. Treatment is based on systemic corticosteroids, potassium iodide, colchicine, NSAIDs and adjuvant compression therapy. Relieving the affected legs is also recommended [33].

Vascular diseases

The cutaneous form of polyarteritis nodosa (CPAN) is very rare in the course of LCD. In 1970, Dyer *et al*. described 4 cases of CPAN concomitant with LCD [34]. Since then about 13 similar cases have been reported. In the course of the disease, painful nodules along the medium vessels or the presence of livedo reticularis, often followed by ulceration, may occur. These symptoms may be accompanied by fever and joint pain [34-36].

In the course of inflammatory bowel disease, another vascular disease caused by circulating immune complexes may develop. This is leukocytoclastic vasculitis. Skin lesions show high diversity. They mostly affect lower extremities with common coexistence of edema and pain. Therapy is based on systemic corticosteroids [37, 38].

Erythema multiforme

Erythema multiforme (EM) (Figure 4) and its heavier form, called Stevens-Johnson syndrome, occurring in the course of IBD is usually associated with the toxic effect of medications (mainly sulfonamides). However, there are reports that suggest that the inflammation itself can cause intestinal lesions characteristic of EM. The role of immunological phenomena in that process has been underlined [39, 40].

Acquired epidermolysis bullosa

What can also coexist with IBD is acquired bullous epidermolysis (epidermolysis bullosa acquisita – EBA). The pathogenesis of this correlation is unclear. Immune mechanisms have been found contributory in that case and the improvement of skin condition during the remission of bowel disease has been observed [12, 13, 41].

Cutaneous Crohn's disease

This is a rare disease, more common in women. It usually affects adults (average start at the age of 35 years), but pediatric cases have also been reported. Skin lesions may be the first manifestation of the disease. Erythematous and infiltrative plaques are often located within the external genital organs. Skin changes that may be recognized as LCD, which affect extremities but do not spread continually, occur very rarely and are referred to as

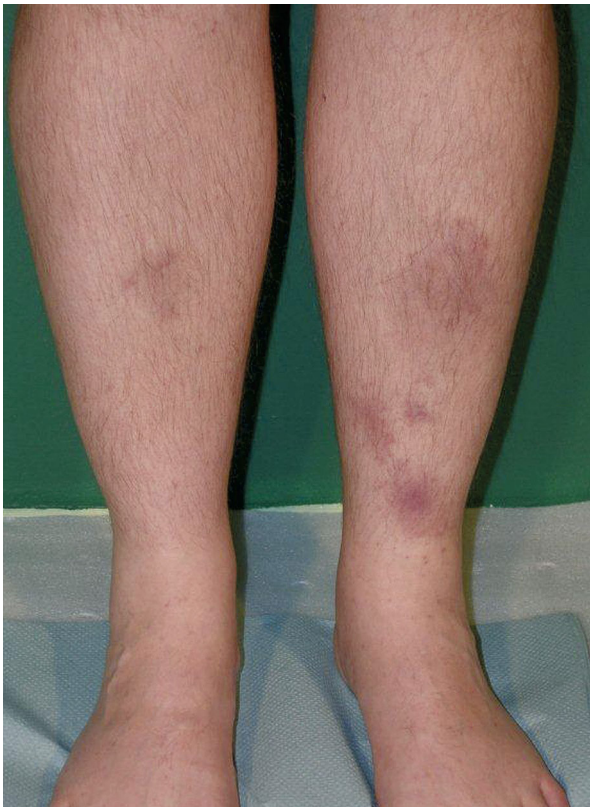

Figure 3. Erythema nodosum

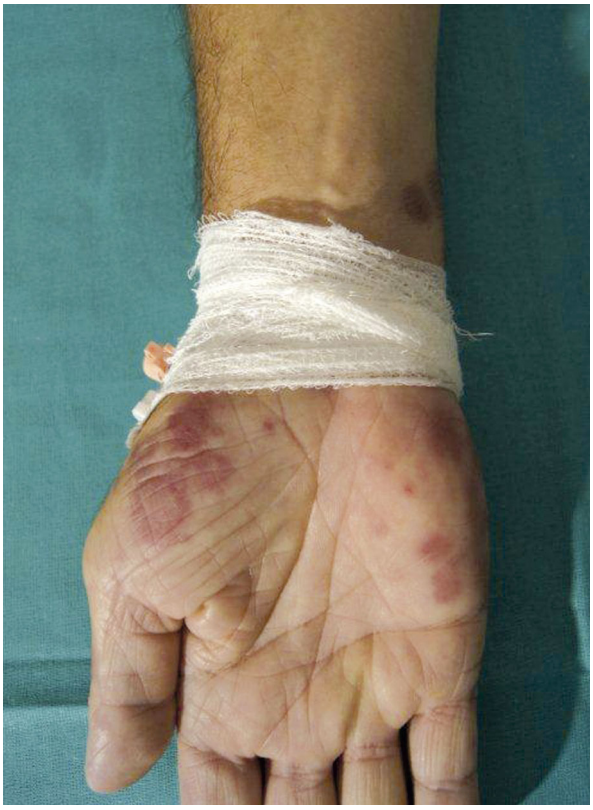

Figure 4. Erythema multiforme

metastatic LCD [3, 18]. In the differential diagnosis, other granulomatous diseases such as tuberculosis, sarcoidosis, fungal infections and reactions to foreign bodies must be considered. Cutaneous LCD is characterized by a chronic course. The severity of lesions correlates with the severity of intestinal changes. The treatment includes a dose of metronidazole 3 × 250 mg per day, often in combination with topical corticosteroids [42, 43]. A systemic therapy of this disease with corticosteroids, sulfasalazine, azathioprine, cyclosporine A and inhibitors of TNF-α has also been reported. Surgical treatment is not recommended [44-46].

As IBD may be accompanied by a wide variety of skin eruptions, patients with inflammatory bowel disease frequently turn to specialists in dermatology for help. Therefore, knowledge of the clinical presentation of skin lesions is absolutely necessary for all dermatologists.

References

1. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations in inflammatory bowel disease [Danish]. Ugeskr Laeger 2009; 171: 3078-83.
2. Christodoulou DK, Katsanos KH, Kitsanou M, et al. Frequency of extraintestinal manifestations in patients with inflammatory bowel disease in Northwest Greece and review of the literature. Dig Liver Dis 2002; 34: 781-6.
3. Glanz S, Maceyko RF, Camisa C, Tomecki KJ. Mucocutaneous presentations of Crohn's disease. Cutis 1991; 47: 167-72.
4. Powell FC, Schroeter AL, Su WP, Perry HO. Pyoderma gangrenosum: a review of 86 patients. Q J Med 1985; 55: 173-86.
5. Karolyi Z, Eros N, Ujszaszy L, et al. Cutaneous and mucosal manifestations of inflammatory bowel diseases. Orv Hetil 2000; 141: 1391-5.
6. Ślebioda Z, Szponar E. Coexistence of lichen planus and ulcerative colitis – a case report. Post Dermatol Alergol 2011; 28: 142-4.
7. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001; 96: 1116-22.
8. Goudet P, Dozois RR, Kelly KA, et al. Characteristics and evolution of extraintestinal manifestations associated with ulcerative colitis after proctocolectomy. Dig Surg 2001; 18: 51-5.
9. Tromm A, May D, Almus E, et al. Cutaneous manifestations in inflammatory bowel disease. Z Gastroenterol 2001; 39: 137-44.
10. Chmiel K, Krela-Kaźmierczak I, Łykowska-Szuber L, et al. Association between dermatological diseases and pathological changes in the gastrointestinal tract. Post Dermatol Alergol 2011; 28: 506-13.
11. Callen JP. Acute febrile neutrophilic dermatosis (Sweet's syndrome) and the related conditions of "bowel bypass" syndrome and bullous pyoderma gangrenosum. Dermatol Clin 1985; 3: 153-63.
12. Gluck M, Kayne A. Acquired epidermolysis bullosa and Crohn' disease. Am J Gastroenterol 2001; 96: 201-2.
13. Livden JK, Nilsen R, Thunold S, Schjønsby H. Epidermolysis bullosa acquisita and Crohn's disease. Acta Derm Venereol 1978; 58: 241-4.
14. Lichtenstein G. Treatment of fistulizing Crohn's disease. Gastroenterology 2000; 119: 1132-47.
15. Pittet V, Juillerat P, Michetti P, et al.; Swiss IBD Cohort Study Group. Appropriateness of therapy for fistulizing Crohn's disease: findings from a national inflammatory bowel disease cohort. Aliment Pharmacol Ther 2010; 32: 1007-16.
16. Present DH. Inflammatory bowel disease workshop. Vail, Colorado, March 22 and 23, 1998. Management of fistula disease. Inflamm Bowel Dis 1998; 4: 302-7.
17. Keshaw H, Foong KS, Forbes A, Day RM. Perianal fistulae in Crohn's disease: current and future approaches to treatment. Inflamm Bowel Dis 2010; 16: 870-80.
18. Coenen C, Börsch G, Müller KM, Fabry H. Oral inflammatory changes as an initial manifestation of Crohn's disease antedating abdominal diagnosis. Report of a case. Dis Colon Rectum 1988; 31: 548-52.
19. Bricker SL, Langlais RP, Miller CS. Oral diagnosis, oral medicine and treatment planning. Gastrointenstinal system B.C. Decker Inc, Hamilton, London 2002; 256-98.
20. Kint A, De Brauwere D, De Weert J, Hendrickx R. Granulomatous cheilitis and Crohn's disease. Hautarzt 1977; 28: 319-21.
21. Ratzinger G, Sepp N, Vogetseder W, Tilg H. Cheilitis granulomatosa and Melkersson-Rosenthal syndrome: evaluation of gastrointestinal involvement and therapeutic regimens in a series of 14 patients. J Eur Acad Dermatol Venereol 2007; 21: 1065-70.
22. Ridder GJ, Fradis M, Löhle E. Cheilitis granulomatosa Miescher: treatment with clofazimine and review of the literature. Ann Otol Rhinol Laryngol 2001; 110: 964-7.
23. Polcz M, Gu J, Florin T. Pyoderma gangrenosum in inflammatory bowel disease: the experience at Mater Health Services' Adult Hospital 1998-2009. J Crohns Colitis 2011; 5; 148-51.
24. Aseni P, Di Sandro S, Mihaylov P, et al. Atypical presentation of pioderma gangrenosum complicating ulcerative colitis: rapid disappearance with methylprednisolone. World J Gastroenterol 2008; 21; 5471-3.
25. Futami H, Kodaira M, Furuta T, et al. Pyoderma gangrenosum complicating ulcerative colitis: successful treatment with methylprednisolone pulse therapy and cyclosporine. J Gastroenterol 1998; 33: 408-11.
26. Ljung T, Staun M, Grove O, et al. Pyoderma gangrenosum associated with Crohn disease: effect of TNF-alpha blockade with infliximab. Scand J Gastroenterol 2002; 37: 1108-10.
27. Wollina U, Haroske G. Pyoderma gangraenosum. Curr Opin Rheumatol 2011; 23: 50-6.
28. Altieri M, Vaziri K, Orkin BA. Topical tacrolimus for parastomal pyoderma gangrenosum: a report of two cases. Ostomy Wound Manage 2010; 56: 56-9.
29. Ali M, Duerksen DR. Ulcerative colitis and Sweet's syndrome: a case report and review of the literature. Can J Gastroenterol 2008; 22: 296-8.
30. Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). Dermatol Ther 2011; 24: 273-84.
31. Farhi D, Cosnes J, Zizi N, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. Medicine (Baltimore) 2008; 87: 281-93.
32. Schwartz RA, Nervi SJ. Erythema nodosum: a sign of systemic disease. Am Fam Physician 2007; 75: 695-700.
33. Gilchrist H, Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. Dermatol Ther 2010; 23: 320-7.
34. Dyer NH, Verbov JL, Dawson AM, et al. Cutaneous polyarteritis nodosa associated with Crohn's disease. Lancet 1970; 1: 648-50.

35. Komatsuda A, Kinoshita K, Togashi M, et al. Cutaneous polyarteritis nodosa in a patient with Crohn's disease. Mod Rheumatol 2008; 18: 639-42.
36. Magnant J, Lhommet C, Machet L, et al. Cutaneous polyarteritis nodosa and Crohn's disease: an association not to be ignored [French]. Rev Med Interne 2009; 30: 345-48.
37. Plaza Santos R, Jaquotot Herranz M, Froilán Torres C, et al. Leukocytoclastic vasculitis associated with Crohn's disease [Spanish]. Gastroenterol Hepatol 2010; 33: 433-5.
38. Zlatanic J, Fleisher M, Sasson M, et al. Crohn's disease and acute leukocytoclastic vasculitis of skin. Am J Gastroenterol 1996; 91: 2410-3.
39. Chapman RS, Forsyth A, MacQueen A. Erythema multiforme in association with active ulcerative colitis and Crohn's disease. Dermatologica 1977; 154: 32-8.
40. Cameron AJ, Baron JH, Priestley BL. Erythema multiforme, drugs and ulcerative colitis. Br Med J 1966; 2: 1174-8.
41. Ray TL, Levine JB, Weiss W, Ward PA. Epidermolysis bullosa acquisita and inflammatory bowel disease. J Am Acad Dermatol 1982; 6: 242-52.
42. Vaid RM, Cohen BA. Cutaneous Crohn's disease in the pediatric population. Pediatr Dermatol 2010; 27: 279-81.
43. Bolognia JL, Joseph LJ, Ronald PR, et al. Dermatology. In: Deramtology. Section 14; 93. Mosby Elsevier 2008; 1433-4.
44. Carranza DC, Young L. Successful treatment of metastatic Crohn's disease with cyclosporine. J Drugs Dermatol 2008; 7: 789-91.
45. Cury DB, Moss AC, Elias G, et al. Adalimumab for cutaneous metastatic Crohn's disease. Inflamm Bowel Dis 2010; 16: 723-24.
46. Palamaras I, El-Jabbour J, Pietropaolo N, et al. Metastatic Crohn's disease: a review. J Eur Acad Dermatol Venereol 2008; 22: 1033-43.