

REVIEW

Cutaneous Manifestations of Inflammatory Bowel Disease

Sophia Georgiou, Efi Pasmatzis, Alexandra Monastirli, Dionysios Tsambaos

Department of Dermatology, School of Medicine, University of Patras, Greece

LIST OF ABBREVIATIONS

IBD: Inflammatory bowel disease

CD: Crohn's disease

UC: Ulcerative colitis

TNF: Tumor necrosis factor

PYG: Pyoderma gangrenosum

NLV: Necrotic leukocytoclastic vasculitis

CNR: Cutaneous nodular pyodermitis

KEY WORDS: *Inflammatory bowel disease, skin, Crohn's disease, ulcerative colitis, pyoderma gangrenosum, vasculitis, pyodermitis*

Address for correspondence:

Sophia Georgiou, M.D.

Department of Dermatology

School of Medicine

University of Patras

P.O. Box 1413 Rio - Patras 26504

Greece

Tel: +30 2610 994 670

Fax: +30 2610 993 951

e-mail: georgiou@med.upatras.gr

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ABSTRACT

Cutaneous lesions are among the most frequent extraintestinal manifestations of IBD. They may precede, occur with or postdate the onset of the intestinal disease and can significantly contribute to the morbidity and impairment of the overall quality of life of the affected patients. In this article, the cutaneous manifestations of IBD are reviewed with particular emphasis on their clinicopathological and therapeutic aspects.

INTRODUCTION

Cutaneous lesions are among the most frequent extraintestinal manifestations of IBD, may in some cases precede the intestinal ones [1,2] and occur in 2%-34% of patients with IBD[3,4], in 5%-44% of patients with CD [5,6] and in 9%-19% of patients with UC [7]. It is the purpose of the present paper to review the most important and common cutaneous manifestations of IBD, with particular emphasis on their clinicopathological and therapeutic aspects.

According to their pathogenetic mechanisms, the cutaneous manifestations of IBD can be classified into the following four categories [7]:

1. **Specific cutaneous manifestations**, whose pathogenesis is identical to that of the intestinal disease.
2. **Reactive cutaneous manifestations**, which are caused by immunological mechanisms triggered by antigens shared by the gut and the skin.
3. **Cutaneous disorders commonly associated with IBD** and
4. **Secondary cutaneous manifestations**, which are due either to complications of IBD or to adverse reactions of the treatment.

SPECIFIC CUTANEOUS MANIFESTATIONS OF IBD

- a. **Perianal fissures and fistulae:** These are usually multiple, represent the most common skin lesions of IBD, occur mainly in CD (20%-60%) and are relatively rarely found in patients with UC [8,9]. They are due to direct involvement of skin and mucosae by the process causing the intestinal disease [10] and may precede the symptoms and signs of the latter by several years [9]. More commonly they affect the perineum, the perianal region, the peristomal and the abdominal wall and often lead to the formation of abscesses, draining sinus tracts, undermined ulcers (that may destroy the anal sphincter) and edematous skin tags due to inflammation

of anal Morgagni's crypts [7,9]. Fissures are commonly painless and posteriorly located, whereas fistulae arise either subsequent to a cryptoglandular infection or as a secondary complication of anal fissures.

- b. **Orofacial CD:** It occurs in 5%-20% of patients and may precede the typical gastrointestinal symptoms by several months or even years. Its manifestation and severity do not always correlate with either the activity of the underlying intestinal disease or its response to treatment [11]. The clinical spectrum of orofacial CD manifestations includes nodules of the gingiva and alveolar mucosa, multiple aphthae-like lesions and, occasionally, linear ulcers, cobblestone appearance of the buccal mucosa, angular cheilitis and ulceration, pyostomatitis vegetans, granulomatous cheilitis, indurated fissuring of the lower lip, gingival hyperplasia and bleeding and diffuse oral swelling [10]. The differential diagnosis of orofacial CD includes sarcoidosis, angioedema, Miescher's cheilitis, cheilitis glandularis and tuberculosis [12].
- c. **Cutaneous (metastatic) CD:** It is a rare and difficult to diagnose disorder most commonly affecting adult females with established intestinal CD. Its symptoms and signs can precede those of the latter by several months or years [10]. It is usually located on the extremities and the intertriginous areas but can occur anywhere on the body. There is no consistent correlation between the occurrence of the cutaneous lesions and the activity of the intestinal disorder [13] or its response to the treatment [14]. Cutaneous CD can be divided into two main clinical forms, the genital (56%) and the nongenital form (44%). The former more commonly occurs in children and is characterized by erythema, edema and fissures or ulcers of the labiae, scrotum or the penis [1,10,15-17]. The nongenital form reveals a polymorphous clinical picture consisting of papules or nodules, plaques with or without ulceration (Fig. 1), abscesses, draining sinuses, hidradenitis suppurativa, lobular panniculitis and scars [15,18-20]. The most commonly affected sites are lower extremities and soles (38%), trunk and abdomen (24%), upper extremities and palms (15%), face and lips (11%) and intertriginous areas (8%) [10]. Although the manifestations of cutaneous CD are mostly characterized by chronic course, in some cases they subside either spontaneously or subsequent to treatment [10,21]. In their clinical differential diagnosis a wide spectrum of diverse disorders (Table 1) should be considered. The confirmation of the clinical diagnosis is based on the histological features, which are identical to those of CD [22].

HISTOPATHOLOGY

The histological features of the specific cutaneous manifestation of IBD are characterized by non-caseating granulomas with multinucleated giant cells mostly occurring in the dermis



FIGURE 1. Clinical features of cutaneous (metastatic) Crohn's disease.

TABLE 1. Clinical and histological differential diagnosis of cutaneous Crohn's disease (CD)

Infections
Mycobacterial infections
Tuberculoid leprosy
Cutaneous mycoses
Lymphogranuloma venereum
Granuloma inguinale
Schistosomiasis
Erysipelas
Granulomatous disorders
Cutaneous sarcoidosis
Cheilitis granulomatosa
Necrobiotic granuloma annulare
Zirconium granuloma
Foreign body reactions
Berylliosis
Miscellaneous
Hidradenitis suppurativa (acne inversa)
Obstruction-induced chronic lymphedema

and only rarely in the subcutaneous tissue, which are surrounded by lymphocytes, plasma cells and some eosinophils. The presence of the latter is characteristic for the granulomatous inflammation in CD, which in some instances is accompanied by small necrotic foci and extensive necrobiotic areas at the central and the peripheral parts of granulomas, respectively [10,20]. Histologically, the specific cutaneous manifestations of IBD have to be differentiated from the disorders included in Table 1.

PATHOGENESIS

The exact pathogenetic mechanisms of the specific cutaneous manifestations of IBD at the molecular level remain presently unknown; however, it seems likely that vasculitis caused by the activation of an excessive immunological response

to antigens released subsequent to damage of the intestinal mucosal barrier in genetically predisposed patients may be responsible for the occurrence of the cutaneous and the other extraintestinal manifestations of IBD [20,23].

TREATMENT

Apart from the management of the underlying intestinal disease, the treatment of the specific cutaneous manifestations of IBD includes the following modalities:

I. Perianal fissures

In our Department, the mainstay of the treatment of perianal fissures is the topical application of glycerine trinitrate 0.2% ointment [24] followed in several cases by symptomatic lesions by botulinum injections into the anal sphincter. In rare cases, showing only limited response to these compounds, calcium channel antagonists (diltiazem) or lateral internal sphincterotomy [25,26] should be considered.

II. Perianal fistulae

Surgical treatment is indicated for type I fistulae, which occur in intestinal areas affected by active CD and includes fistulotomy (particularly for low fistulae), use of flaps and interposition grafts, resection of proximal intestinal disease. Proctectomy and proctocolectomy should be performed in cases with severe perianal disease and rectal involvement [25,27,28].

Conservative pharmacologic treatment is indicated in cases with type II fistulae, which occur in patients with an apparently normal intestinal tract [27] or in those with anastomosis, and mainly consists of systemic antibiotics (metronidazole, ciprofloxacin). In patients unresponsive to the antibiotic therapy, administration of immunomodulators (cyclosporine, mercaptopurine, azathioprine, methotrexate, infliximab) and oral thalidomide should be carefully considered. Only in very rare cases may perianal fistulae favourably respond to systemic steroids, aminosalicylates or mycophenolate mofetil [25].

III. Orofacial CD

Particularly in children, infliximab infusions are the mainstay of the treatment and lead to rapid remission [11]. Alternatively, clofazimine, steroids, immunosuppressants or thalidomide could be used [29,30].

IV. Cutaneous (metastatic) CD

According to our experience, oral metronidazole, and intralesional or systemic steroids are the most beneficial drugs for the conservative treatment of this disorder. In recalcitrant cases, administration of oral sulphasalazine, oral azathioprine (as monotherapy or in combination with 6-mercaptopurine), intravenous infliximab, oral zinc sulfate and hyperbaric oxygen should be considered [1,10,15,30-32]. In cases with severe cutaneous ulcers, surgical resection under oral administration

of zinc sulfate is indicated [10].

REACTIVE CUTANEOUS MANIFESTATIONS OF IBD

The reactive cutaneous manifestations of IBD include erythema nodosum, pyoderma gangrenosum, vesiculopustular eruption, pyoderma vegetans, necrotic leukocytoclastic vasculitis, cutaneous nodular polyarteriitis and other neutrophilic dermatoses.

I. Erythema nodosum: It is the most common cutaneous manifestation of IBD occurring in 3%-10% of patients with UC and in 4%-15% of those with CD [2,4,9,15,33], whereas in children it represents the most common extraintestinal manifestation of the disease; most affected patients are women aged 25-40 years [7,9,34]. Erythema nodosum may in some rare cases precede the manifestations of the intestinal disease by several years and can appear in all clinical phases of IBD; however, in about 20% of the patients it occurs during the acute phase [4,35]. In patients with CD, erythema nodosum, is mostly associated with colon involvement. Nevertheless, its occurrence in IBD correlates well with the activity but not with the severity or the extent of the intestinal disease [2,7,15,36].

The clinical picture of erythema nodosum is characterized by multiple, red or violaceous, deep-seated, non-ulcerating and painful subcutaneous nodules (1-3 cm in diameter), which are usually located on the extensor surface of the lower extremities, particularly on that of the tibiae and rarely on the trunk or the upper extremities, reveal a symmetrical distribution and in most cases show a spontaneous remission without scar formation. Erythema nodosum is often accompanied by fever, chills and arthralgia or arthritis. The latter is rarely seen in children, but in adults it may precede the occurrence of the cutaneous lesions by weeks or months [4,9].

Histologically, erythema nodosum is a diaphragmatic panniculitis, which is characterized by inflammatory infiltration of the fibrous diaphragms of the subcutaneous tissue mainly consisting of neutrophils (in the early phase) and of lymphocytes and histiocytes (in the late phase), by acute necrotic vasculitis of the small venules of the diaphragms with thrombosis and extravasation of the erythrocytes or chronic inflammation with edema of the endothelial cells. In some cases, the lobules may be partially or totally affected by fat necrosis and neutrophilic infiltration [9]. Direct immunofluorescence reveals perivascular deposition of immunoglobulins and complement [37].

Although the underlying pathogenetic mechanisms of erythema nodosum remain presently unknown, it is generally thought that the characteristic cutaneous lesions of this disorder are due to an abnormal immunological response activated by the same bacterial antigens which are responsible for the intestinal disease [4,38]. A significant correlation of erythema nodosum and tumor necrosis factor (TNF) gene

polymorphism has been reported [39]. This gene is located in the region of HLA antigens class II (on the short arm of chromosome 6) where genes associated with the occurrence of arthritis, erythema nodosum and iridocyclitis are also located. Thus, it is possible that the genetic transmission of all these genes leads to the manifestation of the overlapping syndrome, which includes arthritis, erythema nodosum and iridocyclitis in patients with IBD [39-41].

The treatment of erythema nodosum mainly targets the underlying flare up of IBD and almost always leads to the remission of the cutaneous lesions [41]. According to our experience, a rapid resolution of the lesions can be achieved in most patients after oral administration of low doses of steroids. Alternatively, non-steroidal anti-inflammatory drugs, potassium iodide, colchicine, cyclosporine, thalidomide or dapsone can be used. In recalcitrant cases, intravenous administration of infliximab and extracorporeal monocyte-granulocyte apheresis combined with oral 5-aminosalicylic acid may be considered [4,41,42].

II. PYG represents the most severe cutaneous manifestation of IBD (2%-3%) which occurs in 5%-12% of patients with UC and only in 1%-2% of patients with CD, whereas about 50% of patients with PYG also suffer from UC [2,4,15,43]. The correlation of PYG with the activity of the underlying intestinal disease is controversial. In about 75% of patients with CD, PYG occurs during the acute phase of the disease [2] whereas in some rare cases it may precede the onset of the intestinal symptoms by years [7,35]. The clinical picture of PYG is usually characterized by the spontaneous or metatraumatic occurrence of erythematous papulopustular lesions (Fig. 2) that are rapidly transformed into painful necrotic ulcers with edematous, violaceous, sharply circumscribed raised borders (Fig. 3), in which necrotic pustules may occur. The lesions are devoid of any bacteria, expand rapidly and heal with scar formation [4,44,45]. The ulcers are single or multiple, unilateral or bilateral and, in some cases, they may cover the total surface of an extremity. They are located on the lower extremities, the trunk, the face, the neck, around abdominal stomata (peristomal PYG) or in surgical incision or trauma sites (pathergy). Apart from its classic ulcerative form, PYG may also occur in one of the following three clinical forms:

- a. **Pustular**, characterized by multiple painful pustules with halo, which are not transformed into ulcers and persist over a period of months.
- b. **Bullous**, characterized by the occurrence of bullae which are rapidly transformed into painful erosions and necrotic ulcers.
- c. **Vegetans**, characterized by a well demarcated superficial ulcer, which is gradually transformed into an exophytic lesion.

The clinical differential diagnosis of PYG includes a wide spectrum of dermatoses the most important of which are summarized in Table 2.



FIGURE 2. Pyoderma gangrenosum (early phase) in a patient with ulcerative colitis.



FIGURE 3. Pyoderma gangrenosum (late phase) in a patient with ulcerative colitis.

The histological picture of PYG is unspecific and depends on the clinical form, the stage of the lesions and the region of the ulcer the biopsy is obtained from. The most characteristic histological feature is a massive inflammatory infiltration in the dermis, which is composed by neutrophils and leads to the formation of abscess, colliquescence and necrosis with secondary thrombosis of the middle and small vessels and extravasation of erythrocytes. The occurrence of necrotic vasculitis (with fibrinoid, necrosis and leucocytoclastic or lymphocytic vasculitis) is not a constant histological feature [43,46].

An excessive immunological response to bacterial antigens absorbed from the gut, due to damage of the intestinal mucosal barrier in genetically predisposed subjects, may be of essential importance for the pathogenetic mechanisms of erythema nodosum. Autoantibodies are thought to be formed against antigens shared by the gut and the hair follicles followed by deposition of immune complexes and complement on the endothelial wall of dermal vessels, bacteremia, abscess formation and hypersensitivity vasculitis [2,43,47]. The marked accumulation of neutrophils seen in the lesions of PYG is the result of a multistage process characterized by a marked increase in the expression and/or release of proinflammatory mediators, chemotactic or inflammatory cytokines and adhesion molecules. The selective occurrence of cutaneous lesions of PYG on the lower extremities is associated with the distinctiveness of local vascularization and the microcirculation pattern which favors the excessive migration of neutrophils to these areas [45,48].

The mode of treatment for PYG depends on the severity

TABLE 2. Clinical differential diagnosis of pyoderma gangrenosum (PYG)

Infections
Bacterial pyoderma
Gummatous syphilis
Deep fungal infections
Mycobacterial infections
Amebiasis
Viral infections
Drug-related
Halogenoderma
Drug reactions
Vasculopathies
Antiphospholipid syndrome
Systemic (or necrotizing) vasculitis
Synergistic gangrene
Neoplasms
Epithelial neoplasms
Lymphomas
Miscellaneous
Factitial ulcer
Insect bite

of the disease and includes the management of the underlying IBD [4]. In our Department, the mainstay of treatment of the localized form of the disease is the intralesional and/or systemic steroid administration [44], whereas other groups topically apply either tacrolimus 0.3% or nicotine 0.5% [43,49-51] with varying success. In our experience, systemic steroids represent the treatment of choice for multiple lesions or the generalized form of PYG and can lead to a 50% reduction in the size of ulcers within one month and to a complete resolution within 3-4 months [9,41,45]. Alternatively, the following compounds can be used:

Cyclosporin [4,9], sulfasalazine and dapsone, which are efficacious in the management of both IBD and PYG [44], azathioprine and 6-mercaptopurine [43], tacrolimus [43,49,52], mycophenolate mofetil [53,54] and infliximab [41,55,56]. Potassium iodate, minocycline, chlorambucil, cyclophosphamide, methotrexate and thalidomide have also been used in the management of PYG with varying success [9,11,57,58]. Recently, leukocytapheresis was reported to lead to a rapid improvement of PYG and the underlying intestinal disorder [59]. Due to pathergy, surgical excision of the skin lesions should be avoided [41].

III. The vesiculopustular eruption is presently regarded as an abortive form of PYG that occurs not only in patients with UC (5%) but also in those with CD (2%) [7,60]. The eruption is localized or generalized, occurs during the exacerbations of the underlying disease and its resolution follows or coincides with the remission of the latter. The clinical picture is characterized by groups of erythematous vesiculopustular lesions (3-5 mm) localized on the trunk, the genogenital region (Fig. 4) and the extremities (without affecting palms and soles), gradually resolving with a post-inflammatory pigmentation. The lesions do not progress into the typical features of PYG possibly due to an impairment of inflammatory response [9].

The histological picture is characterized by interfollicular, subcorneal and intraepidermal neutrophilic abscesses, whereas in the dermis a perivascular infiltrate consisting of eosinophils, lymphocytes and histiocytes can be seen [61]. Treatment of the intestinal disease usually results in the remission of the vesiculopustular eruption; if this is not the case, the latter should be treated with the therapeutic regimens used in the management of PYG [9,60].

IV. Pyodermatitis vegetans (regarded as a clinical form of PYG) and **pyostomatitis vegetans** represent rare cutaneous manifestations of IBD, which primarily occur in patients with UC. Clinically, pyodermatitis vegetans is characterized by pustules whose rapid rupture results in the development of erosions with hemorrhagic and malodorous ground and vegetating exophytic erythematous plaques surrounded by pustules. These lesions are predominantly located in the folds and, in some cases, on the trunk and the extremities and gradually resolve leaving pigmented scars. Recurrences are not uncommon [9]. Pyostomatitis vegetans, which can precede



FIGURE 4. Widespread vesiculopustular eruption in a patient with ulcerative colitis.

IBD by months or years, is characterized by erythema and thickening of the buccal mucosa with multiple pustules and erosions and in some cases by eosinophilia in the peripheral blood. The clinical differential diagnosis of both disorders includes pemphigus vulgaris or vegetans, bullous pemphigoid, epidermolysis bullosa acquisita, bullous drug eruptions, viral infections, erythema multiforme, Behçet's disease and Sweet's syndrome [62].

Histologically, pyodermitis and pyostomatitis vegetans are characterized by a pseudoepitheliomatous hyperplasia with intra- or hypoe epithelial abscesses containing neutrophils and eosinophils. The treatment of pyodermitis vegetans is similar to that of PYG, whereas that of pyostomatitis vegetans consists of topical and systemic steroids and management of the underlying intestinal disease [7,63].

V. NLV and CNR represent rare cutaneous manifestations of IBD. NLV more commonly occurs in patients with UC, whereas CNR is exclusively seen in patients with CD [7]. Both disorders usually occur after the manifestation of the intestinal disease, but in rare cases they may precede the latter by months or years. The clinical course of NLV and CNR usually reveals no correlation with the activity of IBD [7,64]. The clinical features of NLV include palpable purpura, urticarial plaques, nodules, hemorrhagic bullae, necrotic ulcers and rarely gangrene. These lesions are usually located on the lower extremities. In some cases, cryoglobulinemia and systemic signs and symptoms (fever, malaise, myalgia and malleolar edema) may also occur.

Histology reveals a typical leukocytoclastic vasculitis of the post-capillary venules with infiltration by neutrophils, hemorrhage, necrosis of the vascular wall and fibrin deposition [64]. On immunofluorescence, deposition of IgG, IgM and C3 is seen in the walls of the vessels in the upper dermis

of early lesions.

The clinical picture of CNR is characterized by painful erythematous nodules, ulcers and livedo reticularis most commonly located on the lower extremities. Peripheral neuropathy, arthralgia and myalgia may also be seen. On light microscopy, there is a necrotic leukocytoclastic vasculitis of small and middle diameter arteries at the lower dermis and the subcutis with granulomatous inflammation (in patients with CD) [7,64]. Deposition of immune complexes on the arterial walls is most probably involved in the pathogenetic mechanisms of vasculitis. These immune complexes are formed upon direct exposure of immunocompetent cells of the affected mucosa of colon to focal antigens [64]. The treatment of vasculitis mainly includes systemic or oral steroids and management of the underlying intestinal disease.

VI. The most important neutrophilic dermatoses that occur in patients with IBD are **Sweet's syndrome and the bowel-associated dermatosis-arthritis syndrome** [48]. Common feature of these disorders is the occurrence of an aseptic neutrophilic infiltration in the dermis and/or epidermis, the location and severity of which correlate well with the corresponding clinical features [48].

The classical form of Sweet's syndrome primarily occurs in IBD or may appear subsequent to colectomy, most commonly affects women [65] and is characterized by acute febrile onset with painful, edematous and erythematous nodules and plaques on the surface of which vesicles, bullae or pustules may be present (Fig. 5). In most cases, Sweet's syndrome affects patients with respiratory or digestive infection and may be associated with vaccination, inflammatory disorders, myelohyperplastic diseases, neoplasia or pregnancy. In the acute phase, there is a peripheral leukocytosis with > 70% neutrophils, whereas a dense neutrophilic infiltration in the dermis is the cardinal histological feature of the cutaneous lesions. Systemic administration of steroids represents the treatment of choice. Alternatively, sulphone, colchicine and



FIGURE 5. Severe form of Sweet's syndrome in a patient with Crohn's disease.

potassium iodate [65] may be considered.

The bowel-associated dermatosis-arthritis syndrome, originally described as a complication of surgical jejunioileal-bypass for morbid obesity, is known to occur in a milder clinical form also in patients with IBD without intestinal bypass [44,48,66,67]. The clinical picture of this syndrome is characterized by recurrent episodes of fever, rigor, malaise, arthritis and polyarthralgias of the upper extremities and by the occurrence of cutaneous lesions. The latter consist of erythematous, edematous and painful papules and of aseptic vesicles and pustules (2-4 mm in diameter), which are located on the upper half of the trunk and the upper extremities (usually on the deltoid muscle region). These lesions occur in crops, resolve within 1-2 weeks and relapse after 4-6 weeks [7,44]. The clinical differential diagnosis includes Behçet's syndrome, PYG, generalized gonococcal infection, subacute bacterial endocarditis and systemic candidiasis [68].

The histological picture of the skin lesions is characterized by edema of the papillary dermis, mononuclear and eosinophilic perivascular infiltration, intraepidermal pustules, mild or minute alterations of the walls of capillaries and venules without the typical features of leukocytoclastic vasculitis [7,44,48]. Deposition of immunoglobulins and complement is usually observed at the dermo-epidermal junction by immunofluorescence. Deposition of circulating immune complexes in the skin and the joints that are formed due to immunological response against antigenic peptidoglycans of intestinal bacteria is thought to be involved in the pathogenesis of the syndrome, whereas the pathophysiology of the cutaneous manifestations is similar to that of PYG [48,68].

The management of the bowel-associated dermatosis-arthritis syndrome includes the treatment of the underlying disorder and the administration of systemic antibiotics for inhibition of bacterial growth (tetracyclines, metronidazole, ciprofloxacin, trimethoprim-sulphamethoxazole) and of systemic steroids, sulfone, colchicine or sulfasalazine for inhibition of neutrophils [48].

CUTANEOUS DISORDERS COMMONLY ASSOCIATED WITH IBD

a. Acquired epidermolysis bullosa is a rare, chronic, non-inflammatory, autoimmune bullous disorder of the skin and mucosae that predominantly occurs in patients with long standing CD [7,71]. Its clinical picture is characterized by increased skin fragility and formation of bullae, erosions and scars primarily in regions commonly exposed to mechanical trauma (extensor surface of the extremities, fingers and toes). The histological picture is characterized by subepidermal bulla with an inflammatory infiltrate of varying intensity in the dermis. Direct immunofluorescence reveals a linear deposition of IgG along the dermoepidermal junction, which on electron

microscopy is found to be located under the lower part of lamina densa. Immunoblotting shows circulating autoantibodies against the major 290 kDa protein type VII collagen α -chain and the minor 145 kDa protein [72]. The pathogenesis of the disease is linked to autoantibodies of the IgG-isotype against collagen VII, which is a normal constituent of anchoring fibrils and the basal lamina of normal colon mucosa [71]. In patients with co-occurrence of IBD and acquired epidermolysis bullosa, autoantibodies formed in the course of the intestinal disease are bound to collagen VII of intestinal mucosa and cause epithelial damage and unmasking of antigenic epitopes of collagen VII. IgG autoantibodies produced against these epitopes bind to collagen VII of epidermal basal lamina and cause the bulla formation.

Intravenous immunoglobulin represents the treatment of choice particularly for patients with recurrent and rapidly progressive severe and extensive disease [72], whereas the therapeutic response to systemic steroids, dapsone, phenytoin, colchicine or immunosuppressive agents is rather poor. Plasmapheresis or extracorporeal photochemotherapy could be considered only in those rare cases which reveal a partial resolution under systemic steroids.

b. Bullous pemphigoid and linear IgA bullous dermatosis predominantly occur in patients with UC [73] and rarely in those with CD [74]. Bullous pemphigoid is an autoimmune blistering disorder of the skin and mucosae associated with autoantibodies directed against the normal components of hemidesmosomes (BP 180 and BP 230), and predominantly affects the elderly. It is characterized by an initial urticarial eruption, which progressively develops into large and tense, round or oval bullae scattered throughout the body. Histology reveals an eosinophil-rich subepidermal bulla with eosinophilic and lymphocytic perivascular infiltrate in the upper dermis, whereas direct immunofluorescence shows a linear deposition of IgG and C3 to the epidermal side of the basement membrane zone. Treatment consists of oral tetracycline and nicotinamide, dapsone or prednisolone (with or without an immunosuppressant) and in mild cases of topical corticosteroids.

Linear IgA bullous dermatosis is a rare, acquired subepidermal blistering disease characterized by linear deposition of IgA along the basement membrane (on direct immunofluorescence) and by pruritic, symmetric, grouped annular crusted papules, vesicles or bullae particularly on the extensor surfaces of the extremities and on the buttocks. Histology reveals a subepidermal bulla with a predominantly neutrophilic inflammatory infiltrate in the superficial dermis. Oral dapsone is the drug of choice for the treatment of this disorder. Alternatively, oral sulfapyridine, mycophenolate mofetil, colchicines and intravenous immunoglobulins can also be beneficial.

c. Hidradenitis suppurativa (acne inversa). It is a chronic relapsing inflammatory skin disorder of unknown etiopathogenesis, which is characterized by recurrent draining sinuses and abscesses predominantly occurring in intertriginous

areas and on the genital skin [75,76]. It mostly occurs in CD patients with colon involvement after the manifestation of the intestinal disease and is characterized by follicular obstruction and secondary bacterial infection [77]. Histology reveals inflammation and/or abscess of hair follicles with granuloma and sinus tract formation and fibrosis. In our Department, oral administration of isotretinoin represents the treatment of choice for hidradenitis suppurativa. Antibiotics (metronidazole, minocyclin, clindamycin, erythromycin), steroids and anti-TNF agents have only moderate and temporary therapeutic results. Surgical procedures such as excision or drainage are rarely necessary [77,78]. A careful follow-up is required for early diagnosis and treatment of squamous cell carcinoma that may develop in the lesional skin [79].

d. Phlebitis and periphlebitis occur in >30% of patients with UC but are rarely observed in those with CD. Their pathogenesis is thought to be associated with the predisposition for hypercoagulability due to thrombocytosis and increased factor VIII activity observed in patients with IBD. Several cases of cryoglobulinemia and gangrene have been reported in CD, whereas cryofibrinogenemia and arterial thromboses at the fingers, arms and the penis are rare. The histological features resemble those of disseminated intravascular coagulation [9]. The management of these disorders includes standard conservative measures (leg elevation, warm compresses, anti-inflammatory and anticoagulation drugs) and surgical procedures.

e. Erythema multiforme and **urticaria** are observed in patients with IBD either as a hypersensitivity reaction to the intestinal disease or as a side effect of therapy [7]. Erythema multiforme is an acute disease of the skin and mucosae that ranges from a self-limiting cutaneous eruption to a progressive severe mucocutaneous disorder (Stevens-Johnson syndrome). The former is characterized by maculopapules or vesicles with a red periphery and a cyanotic centre (iris or target lesions) localized on the extremities and less often on the trunk and the face. In the severe form, oral mucosae, eyes, skin and anogenital region show extensive bullae with erosions and haemorrhagic crusts. The main histological findings include keratinocyte necrosis of variable severity, hydropic degeneration of basal keratinocytes, intraepidermal vesiculation and lymphohistiocytic infiltrate. Urticaria is characterized by the occurrence of mostly transient and pruritic edematous papules, which on light microscopy predominantly reveal dermal edema and sparse perivascular lymphocytic and eosinophilic infiltrate. Systemic administration of steroids is the treatment of choice for all forms of erythema multiforme and for severe urticaria whereas in mild forms of the latter systemic antihistamines are beneficial.

f. Other disorders occasionally occurring in patients with IBD are **lichen planus or nitidus**, **secondary amyloidosis**, **viticigo** and **psoriasis** [7,15,38]. Psoriasis, in particular, is observed in 8.9% of patients with CD and is thought to be genetically

and immunologically linked to the latter since:

- I. Certain loci identified on chromosomes 3, 4, 6 and 16 are associated with both psoriasis and CD.
 - II. TNF- α and IFN- γ produced by Th1 lymphocytes are involved in the pathogenesis of these two disorders and induce a delayed-type hypersensitivity reaction.
 - III. Psoriasis and CD reveal a favorable response to compounds that target T-lymphocytes or Th1 cytokines, such as TNF-inhibitors or immunomodulatory drugs [80].
- g. In some rare cases, **squamous cell carcinoma and Bowen's disease** can develop on the apparently healthy skin of perianal region or around colostomies or ileostomies or in the perianal skin tags of patients with IBD. The immunosuppression associated with the intestinal disease or with its treatment is involved in the pathogenetic mechanisms of these neoplasms since it favors the carcinogenetic action of HPV [15]. Surgical excision is the treatment of choice for both neoplasms.

SECONDARY CUTANEOUS
MANIFESTATIONS OF IBD

They are due either to the complications of IBD (particularly malabsorption) or to the side effects of the treatment of the intestinal disease.

A. The cutaneous manifestations due to malabsorption include:

1. **Acrodermatitis enteropathica**, which is caused by the reduced serum zinc levels and is manifested as dermatitis on the extremities, alopecia and diarrhea. Dermatitis is characterized by dry, scaly, eczematous or vesiculopustular lesions located around the stomata, on the face, scalp and the anogenital region. Treatment consists of oral administration of zinc sulphate at a daily dose of 220 mg [7,44].
2. **Pellagra** and **scurvy** due to niacin and ascorbic acid deficiency.
3. **Purpura** due to vitamin C and K deficiency.
4. **Stomatitis, glossitis** and **angular cheilitis** due to vitamin B deficiency.
5. **Xeroderma** and **unspecific eczematous lesions** due to essential fatty acid deficiency.
6. **Hair and nail abnormalities** due to reduced amino acid and protein absorption [7].

In all these disorders substitution of the deficient factors leads to a complete resolution of the cutaneous lesions.

B. The cutaneous manifestations due to side-effects of treatment include:

1. **Cutaneous side-effects of drugs used in the treatment of IBD (Table 3).**
2. **Peristomal dermatitis and ulceration:**
 - a. Peristomal toxic or allergic contact dermatitis is due to leakage of the intestinal content, excretions of fistules and to contact with adhesive tapes or detergents [7]. The

TABLE 3. Cutaneous side-effects of drugs used in the treatment of inflammatory bowel disease (IBD)

Drugs	Cutaneous side-effects
5-amino-salicylic acid	Lichen planus, vasculitis, urticaria, edema, (salazosulfapyridine, skin hypersensitivity reaction sulfasalazine, mesalazine, sulfapyridine)
Metronidazole	Fixed and bullous drug eruption, acute generalized pustulosis, linear IgA bullous dermatosis, pruritus, urticaria
Ciprofloxacin	Leukocytoclastic and necrotic vasculitis, toxic epidermal necrolysis, erythema, pruritus, urticaria, phototoxicity, angioedema, erythema multi-forme, fixed drug eruption, Stevens-Johnson syndrome
Azathioprine	Stevens-Johnson syndrome, papular and maculopapular exanthema, urticaria, angioedema, erythema multi-forme, peeling syndrome, squamous cell and Merkel carcinoma, hair loss, pruritus, lymphoma
6-Mercaptopurine	Skin hyperpigmentation, pruritus, hair loss, papular exanthema, bullous reaction, yellow discoloration of skin, nail hyperpigmentation, injection site reactions, ulcerations of oral mucosa
Methotrexate	Vasculitis, pseudolymphoma, ulceration of oral mucosa and skin, papular eruption, bullous dermatosis, onycholysis, toxic epidermal necrolysis, hair loss, pruritus, acne, phototoxicity, squamous cell carcinoma
Cyclosporin	Acne, hypertrichosis, gingival hyperplasia, squamous cell carcinoma, lymphoma, anaphylaxis, verrucae vulgares, sebaceous gland hyperplasia, epidermal cysts, folliculitis, leukocytoclastic vasculitis, purpura
Systemic steroids	Skin infections, dermatitis, xeroderma, purpura, striae, skin atrophy, skin cancer, acneiform eruption, teleangiectases, skin depigmentation, hypertrichosis, Kaposi's sarcoma
Anti-TNF	Leukocytoclastic vasculitis, lichenoid drug eruption, perniosis-like eruption, granuloma annulare, folliculitis, serum sickness, psoriasiform and bullous reaction, erythema multiforme-like reaction, squamous cell carcinoma, systemic lupus erythematosus, necrotising fasciitis, T- and B-cell lymphoma, Kaposi's sarcoma, skin infections, injection site reactions, cutaneous ulcerations, Stevens-Johnson syndrome, eczematid-like purpura
Mycophenolate mofetil	Severe psoriasiform eruption, acne, dyshidrotic eczema, peripheral edema, skin cancer (squamous cell carcinoma, lymphoma) fungal and viral cutaneous infections
Thalidomide	Morbilloform exanthema, urticaria, vasculitis, brittle nails, dry mouth, erythema nodosum, erythroderma, pruritus, pustular eruption, red palms, toxic epidermal necrolysis, purpura, facial and limb edema, exfoliative reactions
Tacrolimus	Pruritus
GMCSF	Maculopapular eruption, injection site reactions
Transdermal nicotine	Pruritus, hyperalgesia, allergic and toxic contact dermatitis

management of this dermatitis includes the topical or intralesional administration of steroids and the use of protective tapes and nonirritating detergents [9].

b. Peristomal ulceration is due to fistula formation, peristomal PYG, infected hematoma or to pressure from a poorly fitting device [81]. Topical application of antibiotics and/or granulocyte-macrophage-stimulating factor and treatment of PYG and fistulae are helpful.

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