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Management of cutaneous disorders related to inflammatory bowel disease

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Abstract

Almost one-third of patients with inflammatory bowel disease (IBD) develop skin lesions. Cutaneous disorders associated with IBD may be divided into 5 groups based on the nature of the association: specific manifestations (orofacial and metastatic IBD), reactive disorders (erythema nodosum, pyoderma gangrenosum, pyodermatitis-pyostomatitis vegetans, Sweet's syndrome and cutaneous polyarteritis nodosa), miscellaneous (epidermolysis bullosa acquisita, bullous pemphigoid, linear IgA bullous disease, squamous cell carcinoma-Bowen's disease, hidradenitis suppurativa, secondary amyloidosis and psoriasis), manifestations secondary to malnutrition and malabsorption (zinc, vitamins and iron deficiency), and manifestations secondary to drug therapy (salicylates, immunosupressors, biological agents, antibiotics and steroids). Treatment should be individualized and directed to treating the underlying IBD as well as the specific dermatologic condition. The aim of this review includes the description of clinical manifestations, course, work-up and, most importantly, management of these disorders, providing an assessment of the literature on the topic.

Keywords Inflammatory bowel disease, skin disorders, treatment

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Introduction

Inflammatory bowel disease (IBD) may be associated with extraintestinal manifestations that involve multiple organs (20-40%) [1]. After musculoskeletal involvement, dermatological lesions are the second most common extraintestinal disorders of IBD. Almost one-third of the patients with IBD develop skin lesions. The etiopathogenesis, classification, and natural history of cutaneous disorders related to IBD are not well defined. Sometimes skin lesions precede the development of gastrointestinal symptoms, but they can occur with or after the onset of IBD. Moreover, there is not always correlation between IBD activity and the onset and severity of skin disorders [2].

Cutaneous disorders associated with IBD may be divided into 5 groups based on the nature of the association: (a) specific manifestations, (b) reactive disorders, (c) miscellaneous, (d) manifestations secondary to malnutrition and malabsorption, and (e) manifestations secondary to drug therapy (see Table 1) [3].

The aim of this review includes the description of clinical manifestations, course, work-up and especially the management of these disorders, providing an assessment of the literature.

Because the incidence of the majority of these disorders is low, no prospective randomized controlled trials, and only a few studies with more than 10 cases, have been published; therefore, recommendations have to be interpreted with caution.

The treatment of the majority of dermatologic conditions associated with IBD is empiric, including topical and systemic immunosupressants, immunomodulatory and biological agents. Many of these disorders improve or resolve with control of IBD activity [4].

An interdisciplinary approach between dermatologists and gastroenterologists plays an essential role in the management of these patients.

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Specific cutaneous manifestations

Orofacial Crohn's disease (OCD) and orofacial ulcerative colitis (OUC)

In Crohn's disease (CD), oral manifestations occur in 8-9% of the patients. They are more common in the pediatric popu-

Table 1 Cutaneous manifestations in IBD [3]

Specific manifestations
• Orofacial Crohn's disease and orofacial ulcerative colitis
• Metastatic Crohn's disease
Reactive cutaneous disorders
• Erythema nodosum
• Pyoderma gangrenosum
• Pyodermatitis- pyostomatitis vegetans
• Sweet's syndrome
• Pyostomatitis vegetans
• Cutaneous polyarteritis nodosa
Miscellaneous
• Epidermolysis bullosa acquisita
• Bullous pemphigoid
• Linear IgA bullous disease
• Squamous cell carcinoma- Bowen's disease
• Hidradenitis suppurativa
• Secondary amyloidosis
• Psoriasis
Manifestations secondary to malnutrition and malabsorption
Cutaneous manifestations secondary to drug therapy

Table 2 Oral lesions in patients with Crohn's disease [8,9]

Pathognomonic:
• Macrocheilia with/without fissuring
• Cobblestoning of oral mucosa
• Linear ulcerations of oral vestibules
• Mucosal tags
Non-pathognomonic:
• Facial swelling
• Perioral erythema
• Angular cheilitis
• Aphthous stomatitis
• Pyostomatitis vegetans
• Diffuse oral edema
• Hyperplastic granular gingivitis

lation [5], and may precede intestinal involvement [6]. When there is oral involvement, the likelihood of other extraintestinal manifestations is greater. CD may appear in the oral cavity as aphthous ulcerations or superficial bleeding ulcers [7]. However, a wide variety of disease-specific oral lesions have been described in patients with intestinal CD (Table 2) [8,9].

CD in the oral cavity usually takes the form of aphthous ulceration of the mucosal surface. Aphthae and mucosal tags are frequently seen if the oral cavity is carefully evaluated in patients with newly diagnosed CD. Deep tissue inflammation occurs uncommonly and may lead to labial, lingual, and facial swelling and fistula formation can result. CD sometimes shows only orofacial manifestations.

In ulcerative colitis (UC) patients, lesions of the oral cavity may appear as aphthous ulcerations, superficial hemorrhagic ulcers or angular cheilitis. In general, oral lesions coincide with exacerbations of the colonic disease. Similar ulcerations may arise on the buttocks, abdomen, thighs and face. Aphthous ulcers or angular stomatitis occur in as many as 5-10% of patients [7].

Indeed, classification of granulomatous orofacial disease is complex (particularly in the absence of inflammation elsewhere) and there is considerable overlap between orofacial CD, Melkersson Rosenthal syndrome, cheilitis granulomatoses, and the other orofacial granulomatosis [9]. Therefore, diagnosis should include tissue sampling of the involved orofacial region for histopathologic examination [10].

Effective treatment for specific orofacial CD has not been defined. Many patients who are found to have OCD manifestations may be completely asymptomatic, since the oral findings are not clinically problematic [11].

Therapy usually involves the use of agents with proven efficacy in enteric CD, including topical and systemic corticosteroids and immunomodulatory agents. A cinnamon- and benzoate-free diet may be the first approach [12]. Symptomatic treatment, including topical anesthetics, such as 2% viscous xylocaine, can help reduce the pain due to aphthous ulcers.

Beclamethasone mouthwashes (0.5 mg dissolved in water, several times a day) bring symptomatic relief. Lip swelling is sometimes helped by topical tacrolimus. Intralesional injection of steroids into swollen lips has been reported [6]. In patients with persistent pain, swelling, and cosmetic disfigurement, the use of immunosuppression at an early point is to be considered. Doses used in conventional CD are employed. There are no reliable outcome data on this approach.

Biologic agents that target tumor necrosis factor (TNF)-α have been established as effective therapies and are now the treatment of choice for enteric fistulizing CD. Case reports have suggested that infliximab and adalimumab [13,14] are effective therapies in orofacial CD [15,16]; orofacial fistula healing and closure have been described [17].

Metastatic CD

Metastatic CD (MCD) is an unusual cutaneous manifestation of CD, which appears as unspecific skin lesions such as plaques, nodules or crusts, which are erythematous and

occasionally indurated or ulcerated. The histological study shows non-caseating granulomas, and there is no contiguity between the skin lesions and the intestinal involvement [18,19].

Lesions are most frequently located in flexures, genitalia and extremities, although lesions may appear in any other area of the skin, either alone or in groups (Fig. 1) [20-22].

MCD is regarded as highly infrequent, although this is only based on isolated case series. It is a condition in which the heterogeneity of its overall appearance and clinical course may delay diagnosis. A clear correlation between the intestinal and the MCD activity has not been found. Mild and transient lesions may be the reason for consultation and may condition treatment [23,24]. Although MCD is well recognized in adults, it is extremely rare in children. It may develop simultaneously or precede gastro-intestinal involvement; most cases of MCD are seen before the diagnosis of gastrointestinal CD is made [23,25].

MCD diagnosis is based on a combination of clinical exploration and skin biopsies in the context of a patient with CD. However, there have been reports of increased diagnostic complexity, in which skin involvement precedes intestinal implication, with even an interval of several years between the two forms of presentation, or where the skin lesions appeared several years after a proctocolectomy [22,26,27].

Other granulomatous skin diseases must be ruled out (Table 3) [28,29]. Some cases have shown good results after surgical treatment of the skin lesion [24]. Medical treatment is based on the use of topical and oral corticosteroids [20,28,29] associated or not with mesalazine [30] and/or azathioprine [14]. In cases that do not respond adequately, treatment with other immunosuppressants (cyclosporine or tacrolimus) [31-33] or biological agents (infliximab or adalimumab) [34-42] is used.

Reactive cutaneous disorders

Erythema nodosum

Erythema nodosum (EN) is a reactive cutaneous process that is most frequently associated with infections, sarcoidosis, rheumatologic diseases, IBD, drugs, autoimmune diseases, pregnancy, and malignancies (lymphomas). In up to 60% of the cases, no underlying cause is found [43,44].

Table 3 Differential diagnosis of the metastatic Crohn's disease [28,29]

- Pyoderma gangrenosum
- Erythema nodosum and Sweet's syndrome
- Fungal or mycobacterial infections
- Foreign body reactions
- Hidradenitis suppurativa
- Tuberculosis
- Sexually transmitted diseases such as syphilis
- Granulomas related to the exposure to beryllium and zirconium
- Sarcoidosis

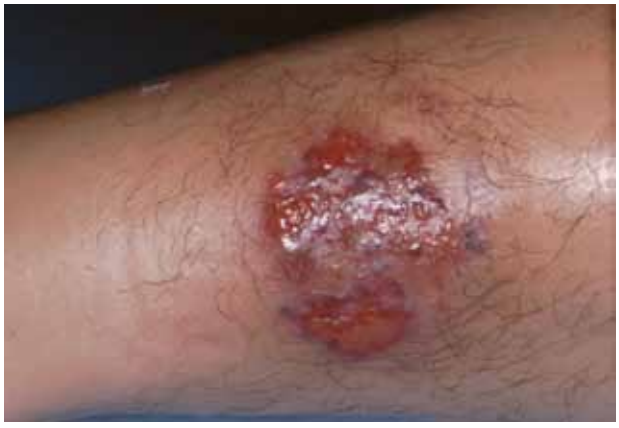

Figure 1 Metastatic Crohn's disease. Ulcerative and crusting lesion

EN is the most common form of septal panniculitis and the most frequent skin manifestation associated with IBD. It has been associated with IBD in 11% of the cases, occurring more frequently in patients with UC than CD. EN is mainly seen in females, and in patients with colonic involvement and/or arthritis, typically associated with an exacerbation of the colitis (90%) but not with the severity or colonic extent, although it may even occur before the diagnosis of IBD [4,44-46].

EN is typically present as multiple, deep-red tender, painful nodules, distributed usually over the shins. The lesions do not show suppuration, ulceration or scarring, and they change to a yellowish color, similar to a deep bruise. Outbreaks appear suddenly and may be accompanied by general symptoms (Fig. 2) [4,45-47].

EN usually regresses spontaneously after a few weeks of supportive treatment with compression stockings, leg elevation, and rest [46]. It sometimes leaves a mild hyperpigmentation

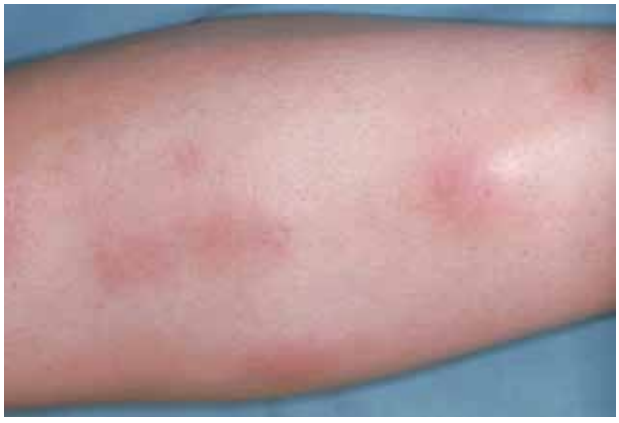

Figure 2 Erythema nodosum. Multiple red, warm, and tender nodules, classically located on pretibial surface of lower extremity

on the skin [44]. When associated with IBD, EN is usually resolved with control of the IBD and often recurs with exacerbations of the bowel disease [4].

Although the first-line therapy is nonsteroidal anti-inflammatory drugs (NSAIDs) [48], they should be avoided in IBD-related EN because they may trigger a flare; if needed, they should be used with caution. More aggressive pain management is reserved for clinical situations that become recurrent or unusually prolonged [43,49]. Intralesional injection of triamcinolone acetonide into the center of the nodules may cause them to heal [44].

Systemic steroids have been advocated as a relatively safe therapeutic option if underlying infection, risk of bacterial dissemination or sepsis, and malignancy has been excluded by a thorough evaluation [49].

Potassium iodide, colchicine, hydroxychloroquine, dapsone, and infliximab have been reported to be successful in treating severe or refractory lesions. Infliximab is highly effective in healing refractory lesions of EN [50]. However, EN has also paradoxically been reported to occur in patients treated with infliximab, with resolution of the lesions upon discontinuation of the medication [48].

Therapeutic agents useful in the treatment of EN have been used to treat IBD-associated EN: cyclosporin A, cyclophosphamide [51], or thalidomide [52]. They may be used in combination with steroids [53].

Other alternative treatments have been tested in patients with UC-associated EN with good results, like proctocolectomy [52] and extracorporeal monocyte granulocytapheresis (M-GCAP) [53].

Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is an idiopathic ulcerative, non-infectious, chronic inflammatory skin disorder of uncertain etiology and belongs to the neutrophilic reactive disease spectrum [54,55]. It is associated with systemic illnesses in 50% of the cases, such as IBD, systemic arthritis, hematological diseases and malignancies.

IBD is the most common underlying disorder and it is found in 10-15% of PG cases, being more frequent (5%) in UC patients. It is typically associated with more severe bowel disease [1] and the clinical course of PG is usually independent of IBD [56].

Characteristic lesions usually begin as a single pustule or vesiculopustule and progress to an ulcer or deep erosion with violaceous overhanging or undermined borders. Lesions are most commonly found on the lower legs. Lesions have been classified into 4 types: ulcerative (typical or classic), pustular, bullous (atypical) and vegetative PG. The diagnosis of PG is based primarily on the clinical presentation and course; histology can also be of value (Fig. 3) [57].

There are currently no standardized treatment guidelines for the management of PG [58]. General supportive therapy and treatment of any concomitant disease have been the standard of care (Table 4).

Local care includes wet compresses with sterile saline solution or Ringer-lactate solution, diluted potassium permanganate solution (1:20000), silver sulphadiazine cream, topical antibacterial creams, and moist dressings (such as hydrocolloid, allograft, Vaseline gauze) to relieve pain, facilitate autolytic debridement, promote re-epithelialization, prevent infections and trauma, and minimize the resulting scar. Occlusive hydrocolloid dressings may also be helpful in superficial ulcers [59], but in case of purulent lesions, semiocclusive dressings are contraindicated [60].

Bioengineered skin dressings may be beneficial in covering ulcers and preventing the need for skin grafts [61-63].

Topical therapy is variable and includes intralesional corticosteroids, topical corticosteroids, 5-aminosalicylic acid [61], sodium cromoglycate, intralesional cyclosporine, tacrolimus [64], pimecrolimus, benzoyl peroxide, nicotine patch, and nitrogen mustard [59,61,62,65]. Recombinant human epidermal growth factor (rhEGF) [66], human platelet-derived growth factor [54,56] and perilesional use of granulocyte macrophage colony stimulating factor [62] have also been reported to be effective. Local irradiation of the lesions, electron beam therapy and hyperbaric oxygen [60,61,65], have also been employed [67]. Topical therapy is most useful in early ulcers or if there are small isolated ulcers. It is usually ineffective as monotherapy, but it can support systemic medication [68].

Systemic treatment may be required for more severe cases or those that are refractory to local treatment. However, the first-line treatment is usually high-dose corticosteroids. In steroid-refractory cases, immunosuppressive drugs have been shown to be effective in individual patients, as well as various new drugs, including biologics.

Systemic therapies are also variable and include sulfa drugs and other antimicrobials such as dapsone, clofazimine, minocycline, and rifampicin, which have been used with different degrees of success. However, the mainstay of systemic treatment is still corticosteroids, administered as bolus doses [69] or in the form of pulse therapy. Other immunosuppres-

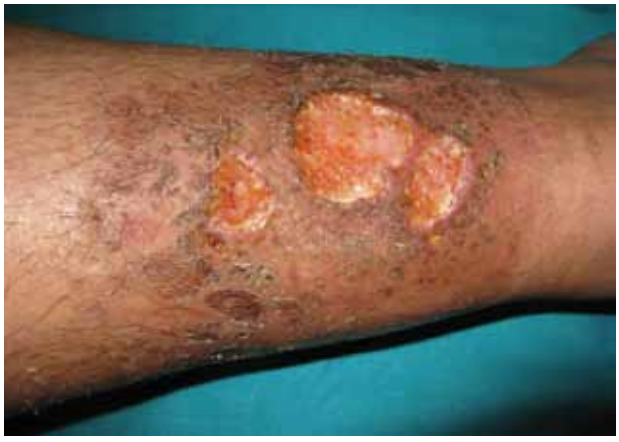

Figure 3 Pyoderma gangrenosum. Painful and irregularly shaped ulcers with violaceous edges

Table 4 Treatments of pyoderma gangrenosum [56-58,60,62]

Drugs	Doses
Corticosteroids	
Topic	
Intralesional	5 mg/mL, twice a week
Systemic	
- Oral (prednisone)	1-2 mg/kg/day, 4-6 weeks
- Intravenous pulses (dexamethasone, methylprednisolone)	1 g/day, 5 days
Immunosupressors	
Cyclosporine	
Intralesional	35 mg in isotonic saline solution, twice a week
Systemic	5-10 mg/kg/day
Azathioprine	100-300 mg/day
5-ASA	
Topic	10%
Systemic	2400-3000 mg/day
6-mercaptopurine	75 mg/day
Cyclophosphamide	100-150 mg/day
Methotrexate	10-30 mg/week
Chlorambucil	4 mg/day
Mycophenolate mofetil	1 g/day
Tacrolimus	
Topic	0.5%
Systemic	0.1-0.15 mg/kg/day
Daunorubicine	60-75 mg/m^2 every 21 days or 20 mg/m^2 3 days every 3-4 weeks. Total dose 550 mg/m^2
Cytosine Arabinoside	Little experience in PG treatment. Has been used at oncologic doses because of associated leukemia
Immunomodulators	
Infliximab	5 mg/kg/day, 0, 2, 6. 8 weeks
Adalimumab	40 mg/week
Etanercept	100 mg/week
Alefacept	15 mg/week
Interferon-alpha (either intralesional or systemical s.c.), subcutaneous dose:	3 MUI 3 times a week
IVIG	2 g/kg/2-3 days
Plasma exchange	
Thalidomide	50-200 mg/day
Antimicrobials	
Benzoyl peroxide (topical)	
Clofazimine	200-400 mg/day
Dapsone	100-200 mg/day
Sulphasalazine	1-4 g/day
Rifampicin	600-1200 mg/day
Minocycline	200-300 mg/day
Vancomycin	500 mg/day
Mezlocilin	200-300 mg/kg/day
Doxycycline	100-200 mg/day
Colchicine	1-2 mg/day
Heparin	
Nicotine gum	6 mg/day
Sodium Cromoglycate (topical)	2% solution, 3 times/day
Hyperbaric oxygen therapy	45-300 minutes or fan oxygen pressure of 2-3 atm

ASA, aminosalicylic acid; IVIG, intravenous immune globulin; atm, atmospheres

sant agents in use include cyclophosphamide, azathioprine, chlorambucil, cyclosporine [70,71], mycophenolate mofetil [63], methotrexate, mercaptopurine, FK506 (tacrolimus) [72] and biologics in refractory cases of PG. Systemic combination therapy with oral or pulse intravenous corticosteroids and/or cyclosporine or azathioprine should be considered as first line therapy [54,73].

Other systemic treatments have also been used with varying success: plasma exchange [56], leukocytapheresis [60,74], intravenous immune globulin, interferon-α, potassium iodide, alefacept [55,56], cytosine arabinoside and daunorubicin, and *Tripterygium wilfordii* multiglycoside [62].

TNF-α inhibitors have improved and broadened the therapeutic options for IBD and have brought new perspectives to the treatment of patients with PG [75]. Three agents have been used in the treatment of PG: infliximab, adalimumab [76-78] and etanercept [79]. The effectiveness of infliximab for IBD-associated PG is reported in many articles [80-82] and a randomized placebo controlled trial showed a significant clinical response rate of PG to infliximab infusions. TNF-α inhibitors are used alone or in combination with azathioprine [83] or methotrexate [84].

Surgical treatment is useful only in extreme conditions because it can be complicated by pathergy in patients with PG [65,85]. Any surgical procedure has to be done as an adjunct measure to immunosuppression, and only in patients with stable disease or partial remission [60]. Options include split-skin grafts and autologous keratinocyte grafts [4,63].

Resolution of penile PG has been reported with therapeutic colectomy in ulcerative colitis [86]. Because the course of PG can be independent of the course of IBD and has even been reported years after proctocolectomy, bowel resection is not a primary therapy [4,56].

The prognosis is that of the associated disease. The control of the intestinal condition can resolve the skin problem and recurrences may occur at periods of exacerbation of IBD. In those patients who readily respond to treatment, the prognosis of the disease is good, but considerable scarring and disfigurement may eventually result [56].

Pyodermatitis-pyostomatitis vegetans

Pyodermatitis-pyostomatitis vegetans (PPV) is a benign and rare mucocutaneous dermatoses often associated with gastrointestinal disorders, especially with IBD. Some authors consider PPV in the spectrum of neutrophilic dermatoses, and others suggest that it is a form of PG [87,88].

There is a strong association of PPV with IBD, particularly with UC. Usually, the intestinal disease precedes the onset of oral lesions by months or years, but oral involvement in IBD could be previous or simultaneous to the gastrointestinal symptoms. The clinical course of oral lesions parallels the activity of IBD. There is general consensus that the bowel should be investigated in PPV, even if intestinal symptoms are absent at presentation [87-91].

Clinically, oral and cutaneous lesions are characteristic and distinctive (although any mucosal surface can be involved). Oral examination reveals multiple, non-painful, small yellowish pustules on an erythematous and edematous base; they rupture easily, producing an elongated superficial aspect, called "snail track" erosions. Cutaneous lesions are characterized by vesiculopustular, exudative, vegetating, annular plaques frequently affecting the scalp, axillae, and groins. Often, skin lesions of PD-PSV appear at the same time as or shortly after the oral disease [87-93].

Oral biopsy is important in establishing a correct diagnosis of the disease. Peripheral blood eosinophilia is associated in 90% of cases [87,91]. The differential diagnosis includes mainly pemphigus vegetans (the condition may also be caused by zinc deficiency) [88,91,92].

Management of PPV depends on the presence of coexisting IBD. The first course of action is the treatment of the underlying condition, which is usually sufficient to control oral and skin lesions.

Various treatments for PD-PSV have been reported, such as topical and oral corticosteroids, and systemic corticosteroids combined with antibiotics, sulfonamides, dapsone, sulphamethoxypiridazine, azathioprine, cyclosporine A or etanercept. The treatment of choice is systemic corticosteroids, starting with moderate to high dosage [91-94]. Bens et al reported that three injections of infliximab and successive maintenance therapy with methotrexate caused a rapid and complete regression of both the PV and the CD [95]. Multivitamin complexes and nutritional supplements can be provided [96]. Surgical treatment in severe cases IBD involves total colectomy and has resulted in complete remission of symptoms.

The oral lesions can be managed with local therapies using antiseptic mouthwashes, tetracycline mouth rinses, and topical corticosteroids. Treatment with topical tacrolimus ointment for PD-PSV has been beneficial in some patients [94]. However, local therapy is generally insufficient [95,97,98]. Unfortunately, the lesions can recur when treatment is tapered or stopped [88].

Sweet's syndrome

Sweet's syndrome (SS) (or acute febrile neutrophilic dermatosis) is a reactive neutrophilic dermatosis. It may be associated with infection of the upper respiratory tract and/or gastrointestinal tract, IBD, pregnancy, cancer, medications and connective tissue diseases [55,99].

The syndrome has been reported as an unusual extra-intestinal manifestation of IBD, principally associated with CD and less commonly with UC [99,100]. In these patients, SS is more common in women, with colonic and perianal involvement, and in patients with other extra-intestinal manifestations [101,102].

The skin manifestations of SS appear concurrently with the relapse of CD (75% of the cases) although SS may also precede or follow the digestive symptoms by many years. It has been also described after proctocolectomy [103,104].

Cutaneous lesions may exhibit pathergy and include

a sudden eruption of painful tender red papules, plaques, pustules, or vesicles. They are commonly located on the upper extremities, face and neck. Patients with SS show severe systemic symptoms [99,105,106]. The diagnosis of SS is based on the clinical and histopathological manifestations (Fig. 4) [55].

The onset can be acute with abrupt resolution of cutaneous symptoms upon treatment or the disease can take a chronic, recurrent course. The natural history of untreated SS is the resolution of skin lesions within 6-8 weeks. Recurrences are common [101,107].

Many different treatments have been used in SS, with different rates of success and relapse. Systemic corticosteroids have been found to be the most common first-line therapy in use [105,106,108]. Localized SS lesions may be treated topically with high-potency corticosteroids, and intralesional corticosteroid. Potassium iodide [109] and colchicine [110,111] are also available as first-line agents to treat SS.

Cyclosporine [112] and dapsone [113] have been used as either monotherapy or in combination therapy (usually as corticosteroid-sparing agents). They should be considered as an alternative to corticosteroids in the treatment of severe, steroid-dependent or steroid-resistant SS cases.

Indomethacin [108,114], chlorambucil, clofazimine, cyclophosphamide [115], methotrexate, etretinate, pentoxifylline [116], danazol, intralesional and systemic interferon-alpha [117], aspirin, naproxen and anakinra [118] have been reported to be effective treatment agents in uncontrolled studies and single case reports.

There have been occasional SS patients whose dermatosis has resolved after treatment with antimicrobials, such as doxycycline [119,120], minocycline, tetracycline, penicillin, pyrimethamine, sulfonamide and metronidazole. Some patients benefit from the combination of steroids and metronidazole [99,103,105,121].

Other treatments for SS such as tacrolimus [103] or infliximab have been described, obtaining worse results, in cases of corticosteroid refractory IBD [104,122].

It is useful to consider that azathioprine, a drug used for maintenance of remission in IBD patients, may cause SS, and, therefore, this possibility must be discarded in patients with SS starting azathioprine treatment [103,123-125].

Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa (CPN) is a distinct clinical entity characterized by a chronic, relapsing, benign course and the absence of systemic involvement. Clinically, it presents with painful subcutaneous nodules, erythema and livedo reticularis that mainly affects the lower extremities. Systemic manifestations are usually associated symptoms [126-128]. Ulcers may develop frequently, without altering the clinical evolution [127].

CPN is a rare cutaneous complication in IBD patients; the relationship between CPN and UC [129] or CD is debatable [128,130,131]. The clinical and histopathological findings

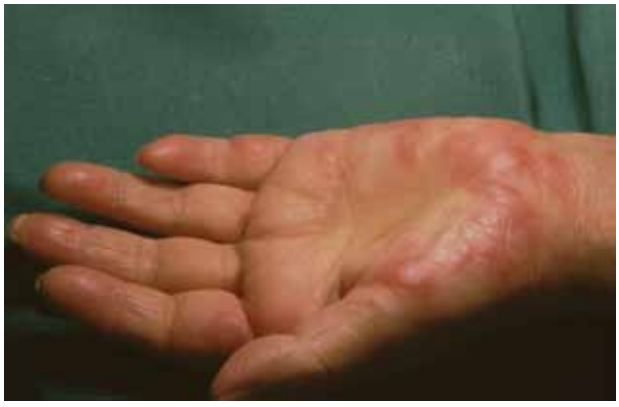

Figure 4 Sweet's syndrome. Painful, red, tender edematous papules with pseudovesiculation

confirm the diagnosis. Treatment is directed toward controlling inflammation and treating any associated systemic illness or infection, but the prolonged course of the disease, with periodic exacerbations and remissions, makes response to treatment difficult to evaluate [126-128].

Low to moderate doses of systemic corticosteroids for 3 to 6 months may induce a remission during an acute flare of the disease. Mild cases can be treated with NSAIDs, like salicylates, alone or in combination with prednisone.

The combination of cyclophosphamide and prednisone results in a good clinical response [129,131,132]. Intravenous immunoglobulins, IFN-α and low-dose methotrexate and other immunosuppressants have also been used [127,132]. A long course of treatment with antibiotics can be effective in patients with streptococcal or other bacterial infections. Sulfapyridine, dapsone, pentoxifyllin and nicotinic acid can also be effective [126,127].

Improvement in cutaneous PAN and CD after treatment with steroids, immunosuppressive agents, aminosalicylates or surgery, has been reported [128], although the course of CPN is considered independent of the bowel disease [133].

Miscellaneous

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is a rare nonhereditary mechanobullous disorder of the skin, characterized by IgG autoantibodies to type VII collagen. IBD is noted in approximately 30% of reported cases of EBA, most of which are CD [134,135]. EBA may present only as a GI disease such as cases restricted to the esophagus. The activity of both IBD and EBA is independent [135,136]; however, an improvement in the skin lesions upon remission of the intestinal involvement has been reported in some cases [136-138].

EBA is often refractory to the conventional treatment approach of high-dose corticosteroids and corticosteroid-sparing agents. Many treatments have been reported with

inconsistent benefits, such as topical corticosteroids, azathioprine, vitamin E, sulfasalazine, mesalamine, phenytoin, gold sodium thiomalate, cyclosporine, colchicine, extracorporeal photochemotherapy, intravenous immunoglobulin (IVIg), mycophenolate mofetil, dapsone, rituximab, and other immunosuppressive medications [134,137-139]. Lehman et al affirmed that conventional therapy with high-dose corticosteroids for long-term has many side effects without consistent benefit and proposed that colchicine or IVIg be considered as first line treatments in mild or advanced cases, respectively [140].

Bullous pemphigoid

Bullous pemphigoid (BP) is an uncommon, chronic, bullous skin disease, mainly affecting the elderly. It is often described in association with other autoimmune disorders and it has seldom been observed in association with IBD [141].

Some authors consider that the autoimmune disorders associations are the consequence of an autoimmune state [142] and the co-existence of ulcerative colitis and BP is more likely to be incidental rather than etiopathogenic [141,143]. Another hypothesis for the association of both disorders is drug-induced BP, such as by mesalamine [141] or sulfasalazine [144].

Clinically, BP is characterized by subepidermal blisters and intensive pruritus. Lesions commonly involve the extremities, lower abdomen, groin, and axillae. BP affects the mucous membranes in about one-third of cases.

The selection of treatment options is based on clinical experience. Oral steroids are considered the standard treatment and they have been used alone or combined; the adjuvant use of immunosuppressant shows some steroid-sparing effect (dapsone and azathioprine). Systemic antibiotics (tetracycline) are needed [141,142,145].

Moreover, colectomy has been reported to ameliorate or even cure immunobullous skin disease in the setting of UC [141], but in another case, improvement was temporary [143].

Linear IgA bullous disease

Linear IgA bullous disease (LABD) is a rare acquired subepidermal autoimmune blistering disorder associated with the deposition of IgA in a linear pattern at the dermoepidermal junction [146,147]. The etiology of LABD is still unknown, although it has been associated with malignancy, autoimmune diseases, infections and drugs. Its association with IBD, particularly UC, has been reported. UC prevalence in LABD patients was 7.1% compared to the 0.05% prevalence in the general population [146-148]. UC usually precedes the onset of the skin disease, although the opposite may also occur [148,149].

Clinical lesions are tense vesicles or bullae. This eruption is usually confined to the skin, but it may involve the mucous membranes in up to 80% of patients [150,151]. Diagnosis of LABD is based on the histopathological and immunopathological findings.

The primary therapy in LABD is still dapsone. Sulfapyridine may be used, if the patient is intolerant to dapsone. Small doses of corticosteroids are often needed in addition to dapsone or sulfapyridine in cases where high-dose dapsone or sulfapyridine alone do not adequately control the disease. Sulfamethoxypyridazine, colchicine, cotrimoxazole, erythromycin, mycophenolate mofetil, oxacillin, dicloxacillin, flucloxacillin, erythromycin, IgIV and a combination of tetracycline and nicotinamide have also been tried with variable results [148,149,151].

Complete remission of LABD after total colectomy for UC has been reported [152].

The course of UC and LABD is not considered to be parallel [146,153], but, in some case reports, both disorders improved after therapy [146,148,153,154].

Squamous cell carcinoma - Bowen's disease

Squamous cell carcinoma (SCC) is one of the most common skin malignancies. Bowen's disease (BD) is an *in situ* form of SCC of the skin [155].

CD and UC have been reported as the cause in a few cases of SCC [156]. The perineal area is the most frequent location of these lesions in IBD, but they can appear at other sites, like photodamaged zones and skin-grafted ileostomy stoma [157]. In patients with CD, SCC was found to be significantly more common (14%) than anal cancer in patients without IBD (1.4%) [158-161].

Cutaneous SCC appears as an erythematous friable papule, plaque, or non-healing ulcer. BD presents with scaly lesions and erythema [162-164].

Most of the squamous tumors develop after prolonged periods [159,165], so it is important to take biopsies in a long-standing perianal IBD with non-healing lesions or when changes in habitual symptoms occur [158,159,166,167].

Surgical excision, with adjuvant radiation in aggressive lesions, is the treatment of choice for most skin SCC and BD [162].

The prognosis of anal carcinoma is generally poor, reflecting the advanced stage at the time of diagnosis; therefore, early diagnosis is essential [168].

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic recurrent disease that usually affects areas of the skin with a high density of apocrine glands (axillae, groin, perianal and perineal regions), characterized by the development of subcutaneous nodules, sinus tracts, fistulae formation, and dermal scarring (Fig. 5). There are reports in the literature associating this condition with CD. The prevalence of HS in UC is unknown [169]. The pathogenesis of this condition is attributed to follicular hyperkeratosis, with occlusion, dilatation, and disruption of

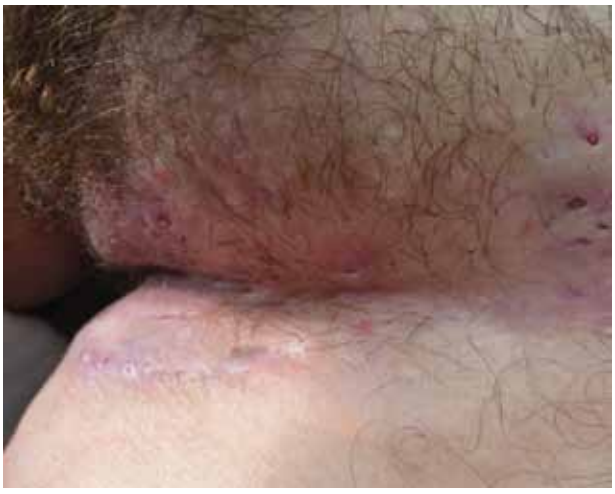

Figure 5 Hidradenitis suppurativa. Subcutaneous nodules, sinus tracts, fistulae formation and dermal scarring

the follicle resulting in local inflammatory response [170]. Medical treatment includes general measures (antiseptic soaps, warm baths, etc.), pharmacological therapy, including local and/or systemic antibiotics, retinoids, and anti-TNF agents, with promising results especially in mild, early-stage disease. Several case reports describe the successful treatment of HS concomitant to CD using anti-TNF-α-agents. Infliximab appears to be an effective medical approach to management and also prepares the patient for "curative" surgery [171-177].

Case series and controlled trials with adalimumab [178] and etanercept obtained favorable results, although further studies are needed for standard practice [179]. Alternative treatment with high dose vitamin B_{12} has been used where conventional therapies have failed [180]. Extensive surgical removal of the affected areas with healing by secondary intention is the appropriate treatment for severe refractory cases [181].

Secondary amyloidosis

Amyloidosis is a clinical condition resulting from abnormal folding of human proteins, which precipitate as insoluble fibrillar polypeptide aggregates in the extracellular tissues, thereby interfering with their normal function. Based on the biochemical nature of the protein itself, systemic amyloidosis had been historically classified as primary (AL) or secondary (AA). AA-amyloidosis is associated to several chronic inflammatory diseases. Systemic amyloidosis is a rare but life-threatening complication of IBD, most cases being reported among CD patients [181-184]. The association of IBD with AL amyloidosis, is very infrequent as it is confined to a case report [185].

The therapeutic approach of these patients should be dual: minimizing the activity of the underlying disease (mitigating or preventing AA production, the precursor of plasma amyloid deposit and responsible for tissue malfunction) and treating the disease once it is established [186]. Although drugs such as azathioprine, colchicine, and dimethylsulphoxide are suggested to delay the progression of renal amyloidosis, their efficacy in patients with high serum amyloid level and acute progression of the renal dysfunction has not been fully elucidated [187].

Case series or single cases treated with TNF-α inhibitors have demonstrated their effectiveness in patients with an acute progression of the renal dysfunction with high serum amyloid levels [188-192].

Psoriasis

Psoriasis is a chronic multisystem, inflammatory disorder which most commonly manifests itself on the skin of the elbows, knees, scalp, lumbosacral and intertriginous areas. Diseases like neoplasms, cardiovascular diseases, IBD and the metabolic syndrome are significantly associated with psoriasis [193,194]. Several studies have described the epidemiological, pathogenic, and genetic association between psoriasis and CD [195-197].

In both diseases, anti-TNF-α antibodies such as infliximab [198-203] and adalimumab [203,204] have a proven beneficial effect. Etanercept has failed to show significant benefit in IBD clinical trials [205]. Novel anti-TNF-α agents, golimumab and certolizumab pegol [206], recently entered the market for the treatment of CD and psoriasis [207]. Several reviews referred to the use of ustekinumab (anti-IL12/23 IgG1 kappa human monoclonal antibody) for the treatment of CD (phase II studies) and psoriasis [208-210].

Non-controlled studies have shown favorable results for tacrolimus and pimecrolimus, (especially for inverse psoriasis) [211], abatacept (T cell co-stimulation blocker) [212], efalizumab (monoclonal antibody targeting CD11a) [213].

Manifestations secondary to malnutrition and malabsorption

The cutaneous manifestations due to malabsorption include diseases that are secondary to deficits in vitamins and trace elements. In all these disorders, the substitution

Table 5 Doses supplementation in malabsorption diseases [214-216]

- Zinc: 3 mg/kg/day of elemental zinc. Serum or plasma zinc levels, zinc-dependant enzyme levels and the copper level should be monitored/3-6 months
- Vitamin A: 100000 IU of vitamin administered intramuscularly for one week and monitoring of plasma levels
- Vitamin E: 800-1500 mg (or 40 mg/kg body weight in children)
- Vitamin K
- Iron

of the deficient factor leads to a complete resolution of the cutaneous lesions [3] (Table 5):

- Zinc. Acrodermatitis enteropathica (AE) is a rare, inherited form of zinc deficiency with periorofacial and acral dermatitis (erythematous, dry and scaly patches and plaques that may evolve into crusted vesiculobullous erosive psoriasiform and pustular lesions), alopecia (diffuse, may affect eyebrows and eyelashes) and diarrhea. The skin lesions may become secondarily infected. Glossitis, hair discoloration, paronychia and nail dystrophy are frequent. Skin biopsy may be useful for diagnostic purposes, but the diagnosis is mainly clinical, with the confirmation of low levels of zinc and alkaline phosphatase in plasma. The differential diagnosis includes atopic dermatitis, candidiasis and seborrheic dermatitis [214,215].
- Vitamin A. Vitamin A promotes cell proliferation and differentiation, and its deficiency is manifested by metaplasia of epithelia throughout the body. The skin lesion due to this deficiency is known as "Phrynodermia", which is manifested as follicular hyperkeratosis distributed symmetrically in the dorsal and lateral surfaces of the extremities. It can also cause widespread xerosis and delayed healing [216].
- Vitamin E. Vitamin E deficiency causes a seborrheic-type dermatitis and edema [217].
- Vitamin K. Its deficiency causes bleeding, bruising and petechiae on the skin [216].
- Iron. Iron deficiency causes angular stomatitis, brittle nails with koilonychia, a painful smooth tongue and diffuse alopecia [216].

Table 6 Cutaneous manifestations secondary to drug therapy [3,218]

Mesalamine	Rash (1- 6%), pruritus (1-3%), alopecia (<3%), acne (1-2%), angioedema, edema, erythema nodosum, facial edema, lupus-like syndrome, lymphadenopathy, photosensivity (<1%)
Sulphasalazine	Rash (>10%), pruritus (1-10%), urticaria (1-10%), alopecia, drug rash with eosinophilia and systemic symptoms, epidermal necrolysis, exfoliative dermatitis, Kawasaki-like syndrome, lupus-like syndrome, periorbital edema, photosensitization, polyarteritis nodosa, purpura, skin decoloration, Stevens-Johnson syndrome, vasculitis (<15)
Azathioprine	Cutaneous lymphomas, squamous cell and Merkel carcinoma, erythema multiforme, sarcomas (Kaposi and others), hypersensitivity reactions (exanthema, rash, vasculitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, hair loss, pruritus, lymphoma
6-Mercaptopurine	Skin and nail hyperpigmentation, rash, alopecia, dry and scaling rash, glossitis, ulcerations of oral mucosa
Methotrexate	Reddening of skin, alopecia, rash, photosensitivity, depigmentation or hyperpigmentation of skin, erythema multiforme, lymphoproliferative disorders, Stevens-Johnson syndrome, stomatitis, macular punctate rash
Cyclosporin	Hirsutism (21-45%), hypertrichosis (5-19%), purpura (3-4%), acne (1-6%), brittle fingernails, hair breaking, abnormal pigmentation, angioedema, cellulitis, dermatitis, dry skin, eczema, folliculitis, keratosis, pruritus, rash, skin disorder, skin malignancies, urticaria, squamous cell skin cancer and benign or malignant lymphoproliferative disorders, gingival hyperplasia and hirsutism
Systemic steroids	Skin thinning, purpura, non-melanoma skin cancers, acne, alopecia, hypertrichosis, striae, Kaposi´s sarcoma, bruising, facial erythema, petechiae, urticaria, wound healing impaired
Infliximab	Rash (1-10%), pruritus (7%), allergic reaction, basal cell carcinoma, cellulitis, delayed hypersensitivity (plaque psoriasis), edema, hypersensitivity reactions, lupus-like syndrome, lymphadenopathy, anaphylactic reactions, anaphylactic shock, angioedema, psoriasis (including new onset, palmoplantar purpura, toxic epidermal necrolysis, urticaria, vasculitis (systemic and cutaneous)
Adalimumab	Cellulitis, erysipelas, anaphylactoid reaction, anaphylaxis, angioneurotic edema, cutaneous vasculitis, erythema multiforme, fixed drug eruption, psoriasis (including new onset, palmoplantar, pustular, or exacerbation), urticaria
Ciprofloxacin	Rash (children 2%, adults 1%), injection site reactions, allergic reactions, anaphylactic shock, anaphylaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, hyperpigmentation, moniliasis, petechiae, photosensitivity, Stevens-Johnson syndrome, toxic epiderma necrolysis (Lyell´s syndrome), vasculitis
Metronidazole	Erythematous rash, pruritus, Stevens-Johnson syndrome, urticaria, linear IgA bullous dermatosis, acute generalized pustulosis
Tacrolimus	Skin burning (43-58%, tends to improve as lesions resolve), pruritus (41-46%), erythema (12-28%)
Thalidomide	Dermatitis (fungal 4-9%), pruritus 83-8%), nail disorder (3-4%), aphthous stomatitis, erythema multiforme, erythema nodosum, exfoliative dermatitis, gynecomastia, lymphedema, myxedema, petechiae, photosensitivity, purpura, Raynaud´s syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis
GMCSF	Rash (44%), pruritus (23%), allergic reaction, anaphylaxis, injection site reaction, peripheral edema

Cutaneous manifestations secondary to drug therapy

The cutaneous side-effects of drugs used in the treatment of IBD [3,218] are listed in Table 6.

It is quite frequent to observe changes in the skin or mucosa triggered by the drugs used to treat IBD. The occurrence of these disorders raises questions about whether to continue or discontinue a drug, in part due to the absence of clear guidelines regarding drug-induced skin reactions. Therefore, the decision depends on the characteristics of the eruption, based on the clinical morphology (bullous forms are the most serious and require immediate discontinuation of treatment), extent (localized or generalized) and symptoms (lesions may be asymptomatic or cause severe itching, burning and / or pain) [219].

The timing of skin reactions is often a useful diagnostic tool. In general, the onset occurs within a few weeks of the introduction of the causative drug. If a medication has been taken for many years with no problem, it is less likely to be responsible. When examining a list of medications taken by a patient with a rash, new drugs taken within the previous month are the most likely cause [220].

On visiting a patient with a supposed drug-induced skin reaction, all recently taken medications should be noted, including herbal drugs, vaccines, etc. We should also take into account if the patient has taken the drug previously and the commercial name of the medicine, for various skin reactions (such as some urticarias) are secondary to the excipients [220].

Many aspects influence the appearance and severity of the drug-induced skin reactions. Baumgart et al recently published the characteristics of skin reactions induced by adalimumab in a cohort of patients. They observed that longer disease duration, lower dose induction schedule, and concomitant use of steroids or immunosuppressants were more often associated with an unfavorable skin outcome.

As in all aspects of IBD, a multidisciplinary view of the patient should be undertaken. In Baumgart's study, skin outcomes differed significantly between patients who saw a dermatologist and/or had a dermatological intervention. They recommended consultation with a dermatologist when skin reaction appears in the context of recent administration of adalimumab [221].

Generally, drug-induced side effects disappear on removing the drug, although sometimes specific treatment or no treatment at all is required. For example, to prevent the appearance of skin rash with infliximab, premedication with corticosteroids and antihistamines is recommended. When rash appears, the extent and, especially, the accompanying symptoms, will indicate the need to stop infliximab or not.

Anti-TNF agents have also been reported to induce the appearance of psoriasis or exacerbate a pre-existing disease, even though they are part of the treatment armamentarium for that same disorder. Wollina et al studied patients with rheumatoid arthritis, IBD, psoriasis, etc, who had pustular lesions during TNF-α inhibitor treatment. He observed that they most frequently had psoriasis which disappeared after removing the drug, sometimes by changing to a different anti-TNF, and occasionally just with topical treatment, but that other times cessation of the drug only achieved stabilization of the disease [222].

Some mild skin reactions such as local reddening of the skin at the injection site of methotrexate or adalimumab, do not require treatment. Other side effects like erythema multiforme, erythema nodosum etc, require specific treatment, in addition to removing the responsible drug, as is done in drug-unrelated cases. Case reports of specific drug desensitization have been described. Akahoshi et al reported the successful desensitization of a sulfasalazine-induced skin rash in a patient with UC [223].

In conclusion, dermatologic lesions are frequent in IBD patients, who should be examined for cutaneous alterations upon presentation and during the course of the disease, not only because of the large variety of associated skin disorders, but also because of the different type of medications that are used in the IBD treatment. The long-term toxicity and carcinogenicity of immunomodulators and biologic agents are still being investigated [224]. The etiology of cutaneous disorders associated to IBD is quite diverse and, therefore, treatment should be individualized and directed to treating the underlying IBD as well as the specific dermatologic condition.

The intention of this review has been to offer the therapeutic recommendations for IBD-related skin disorders that are present in the literature. However, in the absence of prospective and randomized studies, treatment should always be individualized and include the multidisciplinary focus of both the Dermatologist and Gastroenterologist.

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