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Cutaneous manifestations in inflammatory bowel disease (Review)

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Abstract. Inflammatory bowel disease (IBD) is defined as a chronic condition characterized by unpredictable relapsing episodes of gastrointestinal inflammation. IBD is not limited to the gastrointestinal tract and should be considered a systemic disease which can involve any organ. Cutaneous manifestations in IBD are frequent and comprise a broad spectrum of diseases, ranging from mild to severe and sometimes debilitating lesions. Some of the cutaneous manifestations can present signs of an underlying intestinal disease, leading to the screening for non-detected IBD even in the absence of symptoms. Cutaneous EIMs are divided into 4 categories: i) Disease-specific lesions that show the same histopathologic findings as the underlying gastrointestinal disease, ii) reactive lesions which are inflammatory lesions that share a common pathogenetic mechanism but do not share the same pathology with the gastrointestinal disease, iii) associated conditions are more frequently observed in the context of IBD, without sharing the pathogenetic mechanism or the histopathological findings with the underlying disease and iv) drug-related skin reactions.

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Abbreviations: CD, Crohn disease; CPN, cutaneous polyarteritis nodosa; EBA, epidermolysis bullosa acquisita; EN, erythema nodosum; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; NV, necrotizing vasculitis; PG, pyoderma gangrenosum; PV, pyostomatitis vegetans; SS, Sweet's syndrome; UC, ulcerative colitis

Key words: inflammatory bowel disease, extraintestinal manifestations, cutaneous manifestations, drug-related cutaneous manifestations, biologic therapy

1. Introduction

Inflammatory bowel disease (IBD) is defined as a chronic condition characterized by unpredictable relapsing episodes of gastrointestinal inflammation. Classically, IBD is subdivided into Crohn disease (CD) and ulcerative colitis (UC), but the distinction among the two is sometimes difficult. Due to the lack of a single test for discrimination, 10% of IBD cases remaining unclassified (1). Although defined by the gastrointestinal inflammation, IBD is not limited to the gastrointestinal tract and should be considered a systemic disease which can involve any organ. Extraintestinal manifestations (EIMs) in IBD patients are defined as inflammatory entities caused by the same processes that drive inflammation in the gut, but which are located outside the intestine (2). The frequency of reported EIMs ranges from 6 to 47% (2) and interestingly EIMs can appear before or after the diagnosis of IBD is made. Vavricka *et al* (3) showed that in 25.8% of the cases, the first EIM occurred before IBD was diagnosed, with a median time of 5 months before the diagnosis. Although they can be located anywhere, EIMs most frequently affect joints, the skin, the hepatobiliary tract and the eye (2). It was shown that EIMs impact significantly the morbidity and mortality in patients with IBB (4,5) and their presence should be a reason to screen for IBD in order not to delay the diagnosis and to promptly initiate therapy.

The skin and oral mucosa are easily accessible for examination and represent one of the important sites for EIMs. Cutaneous manifestation can be the presenting sign of IBD or can develop together with or after the gastrointestinal signs of the disease. They are described in up to 15% of the patients, although there are studies that report a higher rate (6). Cutaneous manifestations are more frequent in CD, being reported in up to 43% of the patients (6,7).

Classically, cutaneous manifestations in IBD were divided into 3 categories: i) disease-specific lesions that show the same histopathologic findings as the underlying gastrointestinal

disease, ii) reactive lesions which are inflammatory lesions that share a common pathogenetic mechanism but do not share the same pathology with the gastrointestinal disease and iii) associated conditions are more frequently observed in the context of IBD, without sharing the pathogenetic mechanism or the histopathological findings with the underlying disease (8,9). Due to the continuous development of therapeutic options for IBD and the risk of cutaneous adverse reactions associated with these treatments, a fourth category of cutaneous manifestations was proposed by some researchers, namely the drug-related cutaneous reactions.

Another classification of the cutaneous manifestations of IBD takes into account the correspondence between the course of the cutaneous disease and the one of the gastrointestinal disease. As a result, we have manifestations which have a parallel course with IBD, others which may or may not parallel IBD activity and finally manifestations with a separate course from IBD (8,9).

The aim of the present review is to summarize the current knowledge on cutaneous manifestations in IBD.

2. Disease specific cutaneous manifestations

Disease specific manifestations are, as mentioned before, lesions that share the same histopathological findings, namely non-caseating granulomas, with IBD. Disease specific lesions are seen only in CD, due to the fact that UC does not extend to external mucous membranes, being confined to the internal gastrointestinal tract (10).

Fissures and fistulae. There is controversy whether fissures and fistulae should be considered cutaneous EIMs or just an extension of the gastrointestinal disease. Perianal fissures and fistulae were observed in 36% of patients with CD and were absent in UC patients (11). It was shown that the presence of colitis is a strong positive predictor of perianal disease compared to patients with small bowel disease only. Chronic oedema and inflammation in fissures and fistulae, lead to the development of perianal cutaneous abscesses, acrochordons, and pseudo skin tags (12).

Oral Crohn's disease. The granulomatous process can extend into the oral cavity in 8-9% of patients with CD (12). Specific oral lesions include a cobblestone appearance of the oral mucosa; deep linear ulcerations; mucosal tags; swelling of the lips, cheeks and face; lip and tongue fissures; and mucogingivitis (13). Moreover, autoimmune changes of the minor salivary glands, and in consequence dry mouth were reported (13).

Metastatic Crohn's disease. Metastatic CD is an extension of the granulomatous pathology to sites which are not in continuity with the bowel. Although it can manifest anywhere, the metastatic lesions are predominantly located on the extremities and intertriginous areas; the face and genitalia are rarely affected (14,15). Metastatic CD presents as plaques, nodules, ulcerations, abscesses and fistulas (8,12). Noteworthy, the severity of metastatic lesions is not correlated with the severity of underlying disease (16) and the surgical resection of the affected bowel segment does not guarantee resolving of the cutaneous lesions (9).

3. Reactive cutaneous manifestations

Reactive cutaneous manifestations are caused by the underlying IBD and do not exhibit similar pathologic features with the gastrointestinal disease, being present in both UC and CD. It is thought that a cross antigenicity between the skin and the intestinal mucosa is responsible for this type of reactions (17).

Erythema nodosum (EN). EN is the most common clinical form of septal panniculitis, the inflammation of subcutaneous fat tissue; and the most commonly described cutaneous manifestation of IBD occurring in 4-6% of patients (12,18). EN is not exclusively associated with IBD, other triggers being infections, malignancies, drugs or even pregnancy (18). Studies show that EN has a higher incidence in CD than in UC and is seen more frequently in young, female patients (9,12,18). EN appears usually in patients with known IBD, however, 15% of the cases may precede the diagnosis of IBD by up to five years (12,18). Moreover, EN is frequently associated with eye and joint involvement, isolated colonic involvement, and pyoderma gangrenosum (PG) (19).

Clinically, EN is characterized by the rapid onset of symmetrical, tender, and red to violet subcutaneous nodules of 1-5 cm in diameter. The lesions are typically located on the extensor surfaces of the lower extremities, particularly the anterior tibial area; the face, trunk, neck and upper extremities are rarely involved. Cutaneous lesions of EN are associated frequently with systemic symptoms such as malaise, fatigue or arthralgia. Diagnosis can usually be made clinically, biopsy being rarely required. If performed, the histopathological exam reveals a septal panniculitis, while direct immunofluorescence reveals perivascular deposits of immunoglobulins and complement, suggesting an abnormal immunological response of common antigens between bowel bacteria and the skin (17). Although EN parallels underlying intestinal disease activity, being associated with IBD flares, severity of EN does not necessarily parallel severity of the IBD flares (20). In the majority of cases, EN is either self-limiting or the appropriate medical treatment of the underlying disease leads to the resolution of the lesions without scaring. Leg elevation, analgesics, potassium iodine, and compressive stockings are supportive treatment methods, while in severe cases, systemic corticosteroids may be required and represent the first-line treatment. Resistant cases or those associated with frequent relapses, may benefit from immunosuppressive therapy such as azathioprine or from TNF antibodies (2,8,12,17,21).

Pyoderma gangrenosum (PG). PG, considered initially an infectious disease, is a cutaneous manifestation of immune system dysregulation (12). PG is most frequently seen in association with a systemic disease, the most common of these associations being IBD (22). The prevalence of PG in IBD varies from 0.4 to 3%, with some studies indicating a higher proportion in UC compared with CD (2,9,12,17,23,24). Conversely, up to 50% of PG patients have underlying IBD (25). PG is more frequently seen in women, and it is associated with familial history of UC, colonic involvement, permanent stoma, eye involvement and EN (19). PG lesions can appear before, at the same time or after the gastrointestinal manifestations of IBD (9).

PG may vary in clinical presentation and course. The lesions are usually preceded by a trauma, phenomenon known as pathergy. The trauma can be minimal and can precede the skin lesions with many years. The typical skin lesion starts as a sterile pustule that rapidly enlarges due to tissue necrosis; painful ulcers then develop, with undermined violaceous borders and purulent cover. The ulcerations can be solitary or multiple, unilateral or bilateral, with dimensions ranging from centimeters to an entire limb. They can expose tendons, muscles, and deep tissues. Healing is usually associated with scarring, cribriform scars being frequently seen. The lesions can affect any part of the body, but are seen most often on the lower part of the legs and adjacent to stomas (26,27). Peristomal PG is rare and occurs near the site of stoma formation after surgical treatment for IBD, most likely reflecting pathergy; risk factors associated with its development are female sex, presence of other autoimmune disorders and increased body mass index (9).

Diagnosis in PG is based on the clinical picture, but investigations may be helpful to exclude other skin conditions such as infections, necrotizing vasculitis, arterial or venous ulcerations, and malignancies. There are no specific features on the histological exam, a perivascular lymphocytic infiltrate accompanied by a prominent dermal neutrophilic infiltrate being seen (27). The correlation between PG and IBD activity is controversial, as it may parallel IBD activity or run an independent course (21).

Therapy should aim at rapid healing of skin lesions because PG can be a debilitating disease. There are no data sustaining the need for different therapeutic strategies in PG associated with IBD, compared with PG associated with other diseases (21). Moreover, PG may resolve with treatment of underlying IBD (2). The mainstay of treatment is immunosuppression. Local therapy with intralesional or potent topical corticosteroids, topical calcineurin inhibitors, topical dapson can be effective in treating early and mild lesions (27). Daily wound care should be performed. In case of refractory, widespread lesions or in case of active associated IBD, systemic therapy should be started. Corticosteroids have been considered the first-line treatment, other options being oral sulfasalazine, dapsone, imunosupresive agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus and mycophenolate mofetil (2,12,21). Response to therapy varies, however, and refractory cases were reported. Tumor necrosis factor α (TNF-α) inhibitors, especially Infliximab and Adalimumab, are highly effective in treating recalcitrant disease and some favor that they should be considered first-line agents in PG treatment. Infliximab should be considered if a rapid response to corticosteroids cannot be achieved, showing usually a prompt response (2,12,21). Adalimumab is also effective, even in non-responsive to Infliximab patients (28). In patients with UC, complete colectomy may be needed but does not guarantee the complete resolution of PG lesions (12). In the particular case of peristomal PG, closure of the stoma might lead to resolution of PG lesions (21). In more than 25% of the cases, PG has a tendency to recur following successful treatment, frequently in the same place as the initial episode, and may require maintenance therapy to ensure continued remission (21,27).

Pyostomatitis vegetans (PV). PV is a rare reactive manifestation of IBD characterized by the presence of pustules, abscesses, ulcerations and vegetative plaques predominantly on the lips and oral mucosa (29). PV can be observed at any age, but its prevalence is higher in the 20-59 years age range, and it is more frequently described in men (29). All PV cases described in the literature have been associated with IBD (12). Moreover, an association with PG of the skin has been reported (12). Although the pathogenesis of IBD is poorly understood, a dysregulation of the immune system is considered the cause (29). PV lesions tend to appear months or years after IBD, but sometimes the gastrointestinal symptoms may be minimal; in these cases the diagnosis of PV should lead to a prompt referral of the patient to a bowel investigation (29).

Clinically, oral lesions appear as multiple friable pustules, with an erythematous and thickened mucosa that often ruptures leading to ulcerations and erosions. Pain and discomfort are variable, while fever and enlarged, tender lymph nodes can be present (29). Eosinophilia is present in most of the cases, and the histopathological exam reveals intraepithelial and/or subepithelial microabscesses composed of eosinophils and neutrophils. Diagnosis is based on the clinical picture, association with IBD, eosinophilia, negative cultures and histological features (29). PV tends to mirror the underlying disease activity and treatment should be focused on the treatment of IBD, essential for sustained response (9). Local treatment with antiseptic mouthwashes and topical corticosteroids can be used in order to obtain temporary relief. Effective systemic treatments include corticosteroids, TNF-α inhibitors, steroid-sparing regimens such as dapsone or azathioprine; complete colectomy is another option (12). As in PG, recurrences after treatment are common (9,12,29).

Sweet's syndrome (SS). Sweet's syndrome or acute febrile neutrophilic dermatosis is part of a group of conditions characterized by the accumulation of neutrophils in the skin. Sweet's syndrome has been rarely associated with IBD, especially with CD and less commonly with UC (30). Besides IBD, Sweet's syndrome can be associated with other systemic diseases, especially malignancies, or can be drug-related (31). SS was only recently recognized as an EIM in IBD (32,33). In the context of IBD, SS appears more frequently in women, between 30 and 50 years of age, seems to be associated with colonic involvement, and other EIMs (30,31). SS parallels IBD activity in the majority of cases, but may precede the diagnosis of IBD or can occur after colectomy (34). The pathogenesis of SS is unclear, type III hypersensitivity, T-lymphocyte dysfunction, or an association with histocompatibility antigens has been suggested as potential mechanisms (21).

Clinically SS is characterized by the acute onset of succulent, tender, red to purple, inflammatory nodules, papules and plaques that can become confluent, accompanied by burning or pain, usually affecting the upper limbs, face and neck. Lesions can be preceded by trauma (pathergy), similar to PG. Skin lesions are typically associated with fever; other symptoms include arthralgias, headache, and fatigue (31). SS can affect other organs besides the skin, including lungs, muscles, joints, liver, kidney and eyes. Leukocytosis and neutrophilia are frequently seen and the histopathological exam reveals

the presence of papillary edema, with a dense neutrophilic infiltrate and leukocytoclasia (31).

Systemic corticosteroids are first-line treatment and usually lead to rapid resolution of the lesions. Immunosuppressive therapy or biological agents should be considered in resistant or highly relapsing cases (21). Of note, azathioprine has been implicated in the development of SS in some IBD patients (35,36).

Oral aphthous ulcers. Oral aphthous ulcers or aphthae represent the most common oral mucosal finding in IBD patients (9). Aphthae are present in up to 20% of the normal population and in up to one-third of IBD patients (9). The clinical picture is the same, consisting of multiple shallow, round ulcers surrounded by an erythematous 'halo' and covered by a fibrinous exudate. In the presence of aphthae, IBD must be suspected even if intestinal symptoms are not yet present (9,12,13). Increased IBD activity is considered a trigger factor for oral lesions, together with stress, food or drug allergies, trauma and nutritional deficiencies (9,12). Diagnosis is based on the clinical picture, although in case of big, treatment resistant ulcer, especially in smokers a biopsy is needed in order to rule out a squamous cell carcinoma. Treatment consists in addressing the underlying cause and local symptomatic therapy with anesthetics and topical corticosteroids (9,12,13).

Cutaneous polyarteritis nodosa (CPN). CPN is a rare cutaneous EIMs of IBD, defined as a chronic, recurring vasculitis of the small and medium sized arteries, localized in the reticular dermis and subcutaneous tissue. Approximately 10% of the CPN cases are associated with IBD, and the diagnosis of CPN can precede occasionally the gastrointestinal symptoms (12). The pathogenesis is uncertain, but an immune complex etiology is suspected (37). Clinically, CPN presents as a tender nodule, located on the lower extremity, mimicking EN, PG, and metastatic CD (12,38). The diagnosis is based on the histopathological exam which shows a localized perivascular infiltrate, with the absence of the inflammation in the surrounding tissue (12). CPN has an independent course of the underlying IBD and treatment is based on low-dose corticosteroids and NSAINs (9,12).

Necrotising vasculitis (NV). Necrotising vasculitis defines a group of diseases characterized by inflammatory lesions of the blood vessels and necrosis of the vessel wall, and is now a recognized feature of a broad range of diseases with different etiopathogenesis (39). NV has been reported in association with IBD (9,12,40-42). Clinically, palpable purpura, which progresses to ulceration and even gangrene, located typically on the legs, is seen. The histopathological exam reveals a neutrophilic infiltrate and nuclear debris in the vessel wall of the postcapillary venules, distinguishing the disease from PG and CPN (39). Usually NV appears after a diagnosis of IBD, although cases with prior development have been reported (40-42). Systemic corticosteroids are the first line treatment, leading in most cases to the resolution of skin lesions (39).

Thrombosis. IBD confers an increased risk of thrombosis, which can manifest as deep venous thrombosis or thromboembolic disease in the dermatologic patient (43). A meta-analysis conducted by Nguyen *et al* (44) showed that IBD patients have a 2.8-fold increased relative risk of a first episode of venous thromboembolism, the risk being similar for CD and UC. Increased risk is correlated directly with disease activity, although thrombosis can occur also during remission (45). Intestinal inflammation leads to the release of inflammatory cytokines and consequently to the development of a prothrombotic state (43). Thrombosis can manifest in atypical locations, such as the axillary and subclavian venous system and appears in younger age group compared with the general population (46). Prevention and treatment are challenging and have to consider the episodic nature of IBD and the high risk of gastrointestinal bleeding in active disease. Use of anticoagulant thromboprophylaxis with low molecular weight heparin, unfractionated heparin, or fondaparinux is recommended for hospitalized patients with IBD in remission or with active flares of IBD without major gastrointestinal bleeding, including patients with minor gastrointestinal bleeding, although the last is often considered an absolute contraindication to anticoagulant therapy (43). For patients with major gastrointestinal bleeding, mechanical prophylaxis is recommended (44). In outpatients with active IBD without previous history of thrombosis, anticoagulant prophylaxis is not recommended, in contrast to those with positive history in which prophylaxis is recommended during flares (43,44).

Epidermolysis bullosa acquisita (EBA). EBA is a rare autoimmune blistering disease caused by IgG anutoantibodies directed against collagen VII, characterized by subepidermal blisters that progress often to scarring in anatomic areas prone to trauma, such as hands and feet (47). EBA has been associated with IBD, collagen VII being the shared antigen. CD has been described in approximately 30% of EBA patients, while UC is reported with a lower frequency (47). EBA is more frequently associated with CD because of the higher incidence of type VII collagen autoimmunity in CD, compared with UC (47). In the majority of cases, the onset of the gastrointestinal symptoms proceeds by years or occurs simultaneously with the skin disease, although mild gastrointestinal symptoms can be overlooked (47). A variety of treatments have been tried for EBA, including dapsone, sulfapyridine, and colchicine in mild forms, and cyclosporine, mycophenolate mofetil, rituximab, intravenous immunoglobulins and extracorporeal photochemotherapy in resistant and severe forms (9).

4. Associate cutaneous manifestations

As mentioned before, associated conditions are more frequently observed in the context of IBD, without sharing the pathogenetic mechanism or the histopathological findings with the underlying disease (8,9). They are likely related to HLA linkage and the chronic inflammatory nature of IBD (17). Psoriasis, vitiligo, eczema, clubbing of the nails and acrodermatitis enteropatica were all included in this category of EIMs (17). Recently, Kim *et al* (48) conducted a study in order to clarify the association between IBD and inflammatory skin diseases and found that rosacea, psoriasis and atopic dermatitis were significantly associated with IBD, whereas the association between IBD and autoimmune skin diseases including vitiligo and alopecia areata were less marked or nonexistent.

5. Drug-related cutaneous manifestations

Treatment of IBD, as in other inflammatory diseases, implies a balance between controlling active disease and complications on one hand and side effects of medication on the other hand (49). Most of the medications used in IBD supress the immune system and are associated with multiple side effects. Gold standard of treatment is represented by systemic corticosteroids, which remain the first line option for the induction of remission in active disease (49). 5-Aminosalicylate medications are widely used, but they are often not sufficient to maintain long-term remission (49). Immune-modulating therapies such as 6-mercaptopurine and methotrexate are used to maintain remission and to prevent immunogenicity to biologic agents. 6-mercaptopurine is associated with alopecia, skin rashes, Sweet syndrome, and skin cancer. Cutaneous and mucosal side effects associated with methotrexate include oral ulcerations, skin ulcerations, mild alopecia, acral erythema, epidermal necrosis, and vasculitis.

In recent years, the use of monoclonal antibody-based or biologic therapy has increased dramatically in the treatment of moderate to severe IBD, both for induction and maintenance of remission in patients with active disease (49). Anti-TNF agents, such as infliximab, adalimumab, golimumab, and certolizumab can be used in IBD. Approximately 25% of the patients treated with anti-TNF agents develop cutaneous side effects, typically months to years after the initiation of the treatment, although some cutaneous reactions can occur as early as one week after the initiation of the therapy (50). It has been shown that smoking, female sex, and CD are risk factors for anti-TNF-induced cutaneous lesions (50). Fortunately, with adequate dermatological treatment the discontinuation of anti-TNF is only rarely required (50). However, interruption is recommended when unbearable reactions persist despite optimal treatment. Worth mentioning is that some reactions need several months to subside after the interruption of the offending drug (51). Taking into account that skin reactions are a consequence of the inhibition of the TNF function in the skin, being class-specific, switching between different anti-TNF antibodies is not a very useful strategy. However, biologic agents from other classes can be an option. Ustekinumab exhibits therapeutic effects on both Th17 axis and psoriasis, it is not associated with xerosis, eczema, psoriasis or palmoplantar pustulosis, and can induce regrowth in patients with extensive alopecia areata (50-52). Vedolizumab could be an option, but exhibits a gut-specific mechanism of action, and has no effects on EIMs (53).

Segaert and Hermans (50) tried to classify anti-TNF skin reactions into the following: xerosis, eczema, psoriasiform dermatitis, psoriasis, palmo-plantar pustulosis, infections, skin cancer, alopecia and others.

Xerosis. Xerosis or dry skin was observed in more than 40% of patients treated with anti-TNF agents, being more frequent in those with atopic background, in older age or during winter season (50,51). Xerosis is frequently accompanied by eczema or psoriasiform eczema (51). Prevention of xerosis implies avoidance of drying skin care products, frequent bathing, and very hot water, and switching to cleansing oils and lukewarm water. Emollients should be used daily, especially in patients with a history of atopic dermatitis or dry skin (50,51).

Eczema/psoriasiform eczema. Cleynen *et al* (51) observed eczema or dermatitis in 23.5% of IBD patients receiving infliximab, while Esmailzadeh *et al* (54), reported it in 16.3% of infliximab-treated patients without cutaneous psoriasis. Moreover, the latter identified a personal history of atopy as a predictive factor for the occurrence of eczema (54). Clinically, poorly defined, scally, pruritic macules or plaques develop, usually with topography reminiscent of atopic dermatitis. Histology shows typical features for eczema, including spongiosis, exocytosis, dermal perivascular infiltration, ruling out psoriasis (51,55). At the same time, aggravation of a previous dermatitis, namely stasis or contact dermatitis, was observed in patients treated with anti-TNF agents (50,56).

Psoriasiform eczema or psoriasiform dermatitis was the most frequently encountered skin reaction by Cleynen *et al* (51), being described in 30.6% of the cases. Psoriasiform lesions present as scaly, erythematous plaques, with an orange-red hue, resembling psoriatic lesions. Psoriasiform lesions are usually located on the scalp and flexural regions mimicking inverse psoriasis, but can also be seen on the face and trunk. Nail involvement is rare (3.3%), and histology shows features of eczema (8,50). The distinction between psoriasiform dermatitis and psoriasis can be clinically challenging. The lack of sharp demarcation, the absence of silvery-white scales, the frequent bacterial superinfection and the rapid response to corticosteroids favour the diagnosis of eczema, and histopathological examination can be performed in doubtful cases (50).

Bacterial superinfection of is a common feature, both of eczema and psoriasiform eczema, leading to oozing or crusted lesions. Differential diagnosis includes skin infections, allergic reactions, and IBD-associated skin lesions (8,50).

Eczema lesions can usually be controlled with topical treatment, without withdrawal of the medication. Topical treatment options include corticosteroids, vitamin D analogues, and ultraviolet therapy, besides the general methods used to prevent xerosis. In case of bacterial infection, a combination of corticosteroid with an antibiotic or a course of oral antibiotics can be used (8,50).

Psoriasis. Psoriasis, characterised by sharply defined orange-red or deep red plaques, covered by silvery-white scales, is rarely described in IBD patients receiving anti-TNF therapy (51). Superinfection is usually absent, and pruritus may or may not be present. Response to therapy is slower than in psoriasiform eczema. Some patients show both psoriasiform dermatitis and psoriasis at the same time. Guttate and pustular psoriasis have also been described (50). A topical combination of a vitamin D analogue and a potent corticosteroid is usually enough to control the disease, but acitretin, methotrexate, or cyclosporine can be used for resistant cases (50).

Palmoplantar pustulosis. Palmoplantar pustulosis, characterised by recurrent crops of sterile pustules evolving into erythematosquamous plaques, is one of the first described skin reaction associated with anti-TNF agents (50). The reaction seems to be related to smoking, but to a lesser extent than the sporadic form. Palmoplantar pustulosis can appear alone, or can be accompanied by chronic plaque type, guttate, or pustular psoriasis of the body or by psoriasiform eczema (50). Smoking cessation, as well as an ultrapotent corticosteroid

combined with salicylic acid or coal tar is prescribed. Acitretin, methotrexate, or oral corticosteroids are used for recalcitrant cases (50).

Skin infections. Infections are the most frequently encountered cutaneous side effect of anti-TNF agents, with a frequency ranging from 12.5 to 57.1% of patients with cutaneous adverse events (50). Bacterial infections were described most frequently, but viral, fungal and even opportunistic infections can be present (50).

Skin cancer. Some studies indicate a moderately increased risk for non-melanoma and melanoma skin cancer in pacients receiving anti-TNF agents (50). Moreover, some melanoma patients experienced explosive metastasis following the initiation of anti-TNF agents (57).

Alopecia. Patients treated with anti-TNF agents can develop both alopecia associated with highly inflammatory psoriasiform dermatitis and alopecia areata. Alopecia areata occurs on non-inflamed skin, usually as patchy alopecia areata, but alopecia areata totalis and universalis were also described. Exacerbation of known alopecia areata, as well as new onset of the disease has been reported (50). An ultrapotent topical corticosteroid can be used in patchy alopecia areata, while in rapidly progressive alopecia, alopecia totalis or universalis, a switch to ustekinumab or vedolizumab should be considered (50).

Other skin reactions. Rare skin reactions associated with anti-TNF treatment include injection site reactions and infusion reactions, cutaneous lupus, lichen planus, vasculitis, granulomatous reactions, acne, rosacea, amicrobial pustulosis, cutaneous lymphoma, and compromised wound healing.

Discontinuation of the causal anti-TNF agent due to cutaneous side effects is recommended only when unbearable cutaneous reactions persist despite optimal dermatological care. Taking into account that cutaneous adverse events are a consequence of the inhibition of the physiological function of TNF in the skin, switching between different anti-TNF antibodies is not very useful.

6. Conclusions

Cutaneous manifestations in IBD are frequent and comprise a broad spectrum of diseases, ranging from mild to severe and sometimes debilitating lesions. Some of the cutaneous manifestations can be the presenting sign of an underlying intestinal disease, leading to the screening for non-detected IBD even in the absence of symptoms. Cutaneous EIMs are divided into 4 categories: i) disease-specific lesions that show the same histopathologic findings as the underlying gastrointestinal disease, ii) reactive lesions which are inflammatory lesions that share a common pathogenetic mechanism but do not share the same pathology with the gastrointestinal disease and iii) associated conditions are more frequently observed in the context of IBD, without sharing the pathogenetic mechanism or the histopathological findings with the underlying disease (8,9) and iv) drug-related skin reactions. Treatment can be challenging and paradoxical skin reactions may occur in response to anti-TNF treatment, leading to a fourth category of skin manifestations, namely drug-related skin reactions.

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MAB and AFV collected the literature. LU, RC, SCS and IC were responsible for the literature review, manuscript drafting and critical revision of the manuscript for important intellectual content. All authors read and approved the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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