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## Cutaneous manifestations in inflammatory bowel diseases

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### Abstract

Inflammatory bowel diseases have a high frequency in Europe. They are chronic disorders that evolve with relapses and remissions. Clinical features include the signs of underlying inflammatory bowel disease and also signs of extraintestinal manifestations. Cutaneous disorders are the most common extraintestinal manifestations associated with inflammatory bowel diseases, which can be dependent on or independent of gastrointestinal disease activity. The main cutaneous disorders are erythema nodosum and pyodermagangrenosum. The pathogenic mechanisms are not fully understood but it seems that related mechanisms are involved in the development of inflammatory bowel diseases and extraintestinal manifestations. Treatment should be aimed at both the cutaneous manifestations and the bowel inflammation.

## Introduction

Inflammatory bowel diseases (IBD) comprise Crohn's disease (CD) and ulcerative colitis (UC). In Europe, there are 2.2 million people suffering of IBD (1). The etiology remains unknown, but studies have shown that environmental, immunologic and genetic factors are involved. CD and UC share similar features regarding their clinical appearance and pathogenesis, however there are some differences. CD may affect any segment of the digestive tract, while UC involves only the colon and rectum (2). IBD are associated with numerous extraintestinal manifestations, the cutaneous disorders being the ones most frequently seen (3). Cutaneous lesions are diverse and sometimes difficult to diagnose.

Cutaneous manifestations can be divided into three categories: specific manifestations, reactive manifestations and manifestations frequently associated with IBD. The specific lesions exhibit the same histopathological characteristics (non-caseous granulomas) as those observed in intestinal mucosa, as they share similar pathogenic mechanisms. Non-specific lesions, also called reactive lesions, are based on immune processes targeting similar antigens located in the gut and skin (3, 4).

## Discussion

### 1. Specific cutaneous manifestations in IBD

#### *Oral aphtae*

Usually, oral lesions are simultaneous with IBD flares. Aphtous ulcers are commonly seen in patients with IBD. Clinically they resemble classical aphtae, but histopathologically granulomatous lesions that are similar to those identified in the gut may be seen. They occur as sharply defined round ulcers, with erythematous margins. The treatment of the underlying bowel disease leads to the remission of the lesions. Topical anesthetics may be applied (5, 6).

#### *Mucosal nodularity*

Oral mucosa is fissured and swollen with a cobblestone-like appearance, the lesions being typically located on the posterior oral mucosa. In the course of the disease painful papules may be

observed which merge and form plaques resulting in speech and eating impairment. There is no evidence of any correlation between the occurrence of these lesions and IBD activity. Topical corticosteroids are useful (6).

#### *Perianal lesions*

Perianal lesions are more frequent in patients with CD than UC, especially in those with colonic or rectal lesions. The lesions may vary from fistulas to abscesses and strictures or deep ulcerations which may damage the perianal sphincter. The possible complications are sepsis and fecal incontinence. Treatment includes antibiotics, azathioprine and biological agents (infliximab) and sometimes surgical procedures are needed (7, 8).

#### *Metastatic CD*

Metastatic CD is the equivalent of Crohn's disease involving the skin. Metastatic CD is a rare granulomatous disease, being more commonly reported in young women (9). The lesions usually consist of papules, plaques or nodules with or without ulceration, located mainly on the limbs and skin folds. The genital area may also be involved, physical examination revealing erythematous, ulcerated and fissured lesions. The diagnosis should rule out other granulomatous diseases such as tuberculosis or sarcoidosis. Metronidazole or corticosteroids may be used. Severe cases may require the administration of immunosuppressive agents or surgery (3, 4).

## 2. Non-specific (reactive) cutaneous manifestations

#### *Erythema nodosum*

Erythema nodosum (EN) is the most frequent cutaneous manifestation associated with IBD, being more commonly observed in patients with UC as compared to patients with CD. EN is a septal panniculitis, with a female predominance. In most cases its etiology remains unknown, but it may occur in the context of systemic diseases such as malignancy, infections (tuberculosis), sarcoidosis, etc. The lesions appear as red painful ill-defined nodules of various dimensions (1-10mm), more accessible to

palpation than direct observation, located generally on pretibial area. Healing is achieved in a few months without scarring. Recurrences are frequent (10, 11).

IBD exacerbation leads to the occurrence or worsening of EN lesions. In patients with Crohn's disease, EN usually appears in those with colonic involvement (12). Studies have shown that polynuclear cells identified in EN lesions release various cellular mediators which play a role in the activation of other cells and in self-activation. The main identified cytokines were IL 8 and IL 6 which were also highlighted in pyodermagangrenosum (PG). Often PG and EN occur simultaneously in a patient, which suggests that there are similar elements involved in their pathogenesis (13). The administration of non-steroidal anti-inflammatory drugs represents the treatment of choice, but in patients with IBD it should be avoided. Systemic steroids and intralesional triamcinolone are effective. Other therapies include hydroxychloroquine, colchicine, cyclosporine, thalidomide and infliximab (14).

#### *Pyodermagangrenosum*

Pyodermagangrenosum is a rare neutrophilic dermatosis in the general population, but it has an increased incidence among persons with IBD. PG is also associated with rheumatological diseases, myeloproliferative disorders and neoplasms. An underlying disease is identified in 50-70% of patients with PG, the association with UC being reported most often. The onset may be before or after the occurrence of IBD signs, but more frequently after it. The course of PG may or may not be influenced by the activity of underlying intestinal disease. Thus cases of PG after proctocolectomy were reported (15, 16). A recent study has shown that on average the onset of PG took place 15 years after the diagnosis of IBD was made and the patients had been diagnosed with IBD at an older age (17).

The mechanism of development of PG is unclear. It seems that it is based on an autoimmune process, auto-antibodies being directed against components of intestinal mucosa and skin. In the pathogenesis, various cellular mediators such as interleukins (IL8, IL16, IL17) and TNF alpha are involved (12). In addition, abnormal responses of lymphocytes and neutrophils impairment were suggested (16). According to some authors, patients with severe IBD are more likely to develop PG and

the course of PG is correlated with IBD flares (8). PG is more common in women, but there are studies emphasizing a male predominance. It was typically reported after a trauma on legs. PG is a debilitating condition, which starts with papules, vesicles or pustules resulting in painful ulcerative lesions with irregular violaceous borders (18).

There are four types of PG: ulcerative, pustular, bullous and vegetative. The ulcerative form is the most common. Histopathologically there is evidence of a neutrophilic infiltrate in the dermis, as the disease progresses an infiltrate consisting of mononuclear cells surrounding areas of necrosis develops (19). The treatment is difficult. Systemic or topical corticosteroids or immunosuppressive agents should be used along with the treatment of the underlying intestinal disease. Therapy of IBD with biological agents proved to be effective for PG lesions (18).

#### *Sweet's syndrome*

The association between Sweet's syndrome (SS), a rare neutrophilic dermatosis and IBD is uncommon; most cases have been reported in women. According to the medical literature, about 40 cases have been described. The majority of patients had colonic involvement and based on this observation scientists raised the hypothesis of the involvement of intestinal bacterial antigens in the disease development (20). The onset of the lesions overlaps IBD flares, but SS may be diagnosed before the diagnosis of IBD or it may occur after proctocolectomy (21). Some authors consider that SS is a type III hypersensitivity reaction or a dysfunction of neutrophils or T cells is involved. The histopathological findings display a neutrophilic infiltrate in the superior dermis. Leukocytoclasia without vasculitis may also be observed. Clinically the lesions vary from papules to nodules, being painful and erythematous, located typically on the cephalic extremity, upper limbs and trunk (22). It is associated with fever and neutrophilia. Patients may present oral stomatitis and oral ulcerations. Corticosteroids are the optimal treatment; methotrexate, cyclosporine, dapsone have been also reported to be successful in the therapy. Relapses are common (23).

*Pyostomatitis/pyodermatitis vegetans*

Pyostomatitisvegetans (PV) is a chronic benign disorder, the equivalent of pyodermatitis vegetans, affecting the mucous membranes, mainly oral mucosa. The diagnosis of PV requires investigations for an inflammatory bowel disease. On oral mucosa the lesions occur as pustules and vesicles which develop into ulceration. Genital, nasal or conjunctival mucosa may be involved (24). Pyodermatitis vegetans is characterized by the appearance of vegetating well-defined plaques (25). In most cases, eosinophilia is present. Histopathologically, abscesses mostly consisting of neutrophils are observed. Several hypotheses on the pathogenesis of the disease have been postulated. The involvement of a microbial agent was presumed but none has been revealed (26). Corticosteroids represent the first-line treatment. They may be administered in combination with antibiotics and immunosuppressive agents. The oral lesions can be alleviated with local corticosteroids and antiseptic solutions (14).

*Leukocytoclastic vasculitis*

Leukocytoclastic vasculitis is a rare disorder encountered in patients with UC, which parallels the evolution of the intestinal disease. The association between the two disorders may be due to the immune complexes formation in both bowels and vessels. Histopathological features exhibit inflammation in the postcapillary venules and nuclear detritus. Sulfasalazine and colchicine may be used as therapeutic options (27).

## 3. Cutaneous manifestations frequently associated with IBD

*Epierythema multiforme acquisita*

Epierythema multiforme acquisita (EBA) is an acquired bullous chronic disease, the main trigger being trauma. It was reported that 30% of patients diagnosed with EBA suffer of IBD. The two diseases evolve independently of each other (14). Usually lesions consist of blisters that occur after an injury of the skin. Subsequently, they heal with scarring and milia formation (28). In patients with EBA, Ig G and Ig A autoantibodies directed against type VII collagen, a component of the basement membrane zone, are identified. Histopathological examination displays subepidermal blisters and inflammatory infiltrate in



the dermis (29). Direct immunofluorescence reveals immunoglobulin deposits within epidermal-dermal junction. Colchicine is the treatment of choice. Cyclosporine is also effective. High doses of corticosteroids, methotrexate, azathioprine or biological agents (rituximab) proved to be useful in the therapy (28).

#### *Linear Ig A bullous dermatosis*

Linear Ig A bullous dermatosis is an acquired autoimmune disorder affecting both children and adults. It manifests clinically as urticarial lesions, with peripheral vesicles or as a bullous eruption with tense blisters that evolve into ulcerations. In most cases the mucous membranes are involved (30). Histopathological findings consist of subepidermal blisters and neutrophilic infiltrate in basement membrane. Direct immunofluorescence shows linear IgA deposits and sometimes IgG and complement deposits along the basement membrane zone (31). The course of the disease is not correlated with the bowel disease activity, symptoms persisting in some cases even after colectomy. Linear IgA dermatosis is more common in patients with UC (32). It is thought that, patients with UC have an increased production of monomeric IgA in colonic mucosa; there is a cross-reaction between lamina lucida and lamina densa antigens. Dapsone is the treatment of choice (30).

#### *Psoriasis*

Studies have shown a higher incidence of psoriasis in patients with IBD in comparison with the general population. It seems that there are similar mechanisms regarding the pathogenesis of IBD and psoriasis, identifying increased levels of TNF alpha in both psoriasis and Crohn's disease lesions (33). In addition, in both diseases Th 17 lymphocytes stimulated by IL 23 play an important role. Involvement of related pathogenic mechanisms is also suggested by the efficiency of infliximab and adalimumab in the therapy of the two diseases (34). Regarding the genetic determinism, it seems that chromosomal loci 6p22, 16q, 1p31 and 5q33 are involved in both diseases (35).

## Conclusions

Cutaneous manifestations may occur before or after the diagnosis of IBD was made. It is important to know the extraintestinal manifestations associated with IBD because their recognition may lead to an early diagnosis of IBD. On the other hand, patients with IBD should be investigated in order to diagnose these cutaneous manifestations. Cutaneous manifestations may or may not be influenced by the disease activity. Sometimes, they are difficult to diagnose, a high degree of suspicion being necessary. Therefore, the association between IBD and multiple cutaneous manifestations must always be kept in mind.

## Disclosure

No authors involved in the production of this article have any commercial associations that might pose or create a conflict of interest with information presented herein.

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