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ORIGINAL ARTICLE

Cutaneous manifestations in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), mainly chronic unspecific ulcerative colitis and Crohn's disease have increased in incidence in the last decades. These have multiple extraintestinal manifestations, with those of the skin appearing after the intestinal clinical presentation. These are classified as: granulomatous dermatosis, reactive dermatosis, and those secondary to treatment of IBD, and other dermatosis. This article presents the pathogenesis, clinical approach, treatment and expected evolution of these manifestations. (Gac Med Mex. 2016;152:557-64)

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KEY WORDS: *Inflammatory bowel disease. Ulcerative colitis. Crohn's disease. Oral ulcers. Erythema nodosum. Pyoderma gangrenosum. Sweet´s syndrome. Malnutrition. Fissures. Fistules.*

Introduction

Inflammatory bowel disease (IBD) has multiple extraintestinal manifestations, including skin manifestations that most times appear after the intestinal clinical presentation, which makes it essential identifying them for an adequate diagnostic and therapeutic approach. In addition, the recognition of dermatological entities may even be able to guide a not-yet-established IBD diagnosis.

Pathogenesis of chronic nonspecific ulcerative colitis and Crohn's disease-associated dermatoses

The incidence of both conditions has increased over the past few decades, especially Crohn's disease (CD), which has an important hereditary component[1]. Skin manifestations actual prevalence is hard to estimate due to diagnostic difficulty, but a prevalence of up to 40% is estimated in 20 to 40-year old patients[2-6].

The presence of human tropomyosin isoform 5 and a colonic epithelial protein in the skin, eyes, biliary tract and joints have been proposed to be targets of autoimmune attacks to extraintestinal organs by these diseases [7].

Classification

Skin manifestations are classified as: granulomatous lesions, reactive dermatoses, dermatoses associated with IBD drug treatment and other dermatoses[8].

In this classification, the most common dermatoses are encompassed (Table 1).

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Table 1. Classification of IBD skin manifestations

Reactive Dermatoses	Granulomatous Dermatoses	Treatment-related dermatoses
Erythema nodosum	Fissures and fistulae	Secondary dermatoses
Aphthous stomatitis	Oral Crohn's disease	Undernourishment/Malnutrition
Neutrophilic dermatoses – Pyoderma gangrenosum – Pyodermatitis and pyostomatitis vegetans – Sweet's syndrome	Metastatic Crohn	

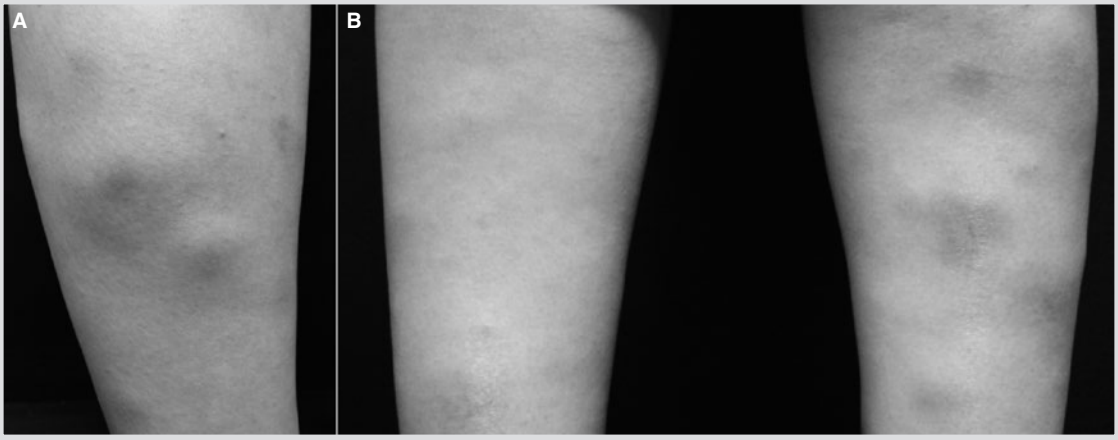

Figure 1. ***A*** *and* ***B****: Erythema nodosum on lower limbs.*

Reactive dermatoses

Erythema nodosum

It is the most common skin manifestation of IBD and is predominant in CD (4-15% incidence vs. 3-10% in chronic nonspecific ulcerative colitis [CNSUC])[9,10]. It occurs mainly in 10 to 30-year old women with Crohn's disease, which suggests an estrogenic component in this inflammatory response[11,12]. Usually, it appears within the first two years of disease onset[13].

Presentation

It has a sudden onset characterized by tender, bilateral and symmetric erythematous nodules of approximately 2 cm in diameter. They appear on the anterior legs but can occur on the posterior legs, trunk, face and outer arms. It is usually self-limiting, in 2-3 weeks[5,14] (Figs 1 A and B).

The diagnosis is clinical[10]. The lesions can change their color to yellowish and resolve spontaneously in 6 weeks. This dermatosis can be accompanied by fever, synovitis and arthritis[15]. In the biopsy of these lesions, septal panniculitis is observed; if it's early, it will consist of neutrophilic infiltrate; if it is late, the infiltrate will be histiocytic; occasionally, there may be fatty necrosis[16]. IBD should be suspected in patients with erythema nodosum; in those with no apparent underlying disease, it is useful obtaining a chest radiography, pharyngeal culture and ASO and/or PPD titers[17].

Treatment

These lesions are self-limiting and have a 6-week duration[18]. Its management is based on systemic steroids or immunomodulators such as azathioprine[19]. As adjuvant treatment, compressive measures, lower limbs elevation and rest are recommended[18]. Potassium iodide can be employed as second-line therapy at

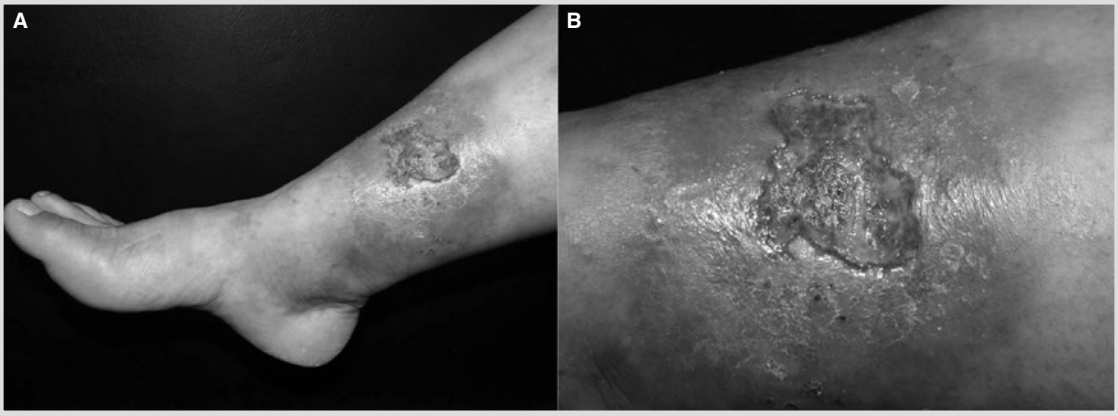

Figure 2. ***A*** *and* ***B****: Ulcerative pyoderma gangrenosum.*

a dose of 900 mg/day with favorable response at one week[20].

If proctocolectomy is performed as treatment for IBD, erythema nodosum is improved[21]. Improvement is quick and is paralleled by treatment effectiveness, with relapse in case of IBD exacerbation[5,14,22]. In treatment-refractory cases, infliximab can be used[23].

Aphthous stomatitis

This condition affects 4.3% of patients with CNSUC and its etiology is multifactorial, with some cases being attributed to nutritional deficiencies secondary to bowel disease activity[5,18]. Lesions are tender, oval or round-shaped ulcers, with yellowish pseudomembrane and erythematous border on oral and labial mucosa, floor of the mouth and tongue[18,24]. The appearance of lesions is abrupt and coincides with a recurrence or exacerbation of the bowel disease[18,25]. They usually last 10-14 days and heal without leaving scars[24]. Minor aphthous ulcers (10 mm) are re-epithelized with no sequels; larger aphthous ulcers are deeper and heal with scarring[18].

Treatment of the underlying disease results in the remission of ulcers, but treatment should be symptom-control oriented[18,26]. Antiseptic mouthwashes with chlorhexidine, tetracycline (250 mg in 5-10 ml of water) can be used, which reduces pain due to decreased bacterial colonization of ulcers, in addition to ointments or gels that provide a protective barrier[24]. Prednisone or dapsone can be used as systemic treatment. For patients whose manifestations are refractory to all the above, thalidomide at 50-150 mg/day doses can be initiated[27].

Pyoderma gangrenosum (PG)

Presentation

It starts with a nodule or erythematous pustule that evolves into a painful ulcer with irregular, undermined, violet-colored borders. In spite of their dramatic appearance, these ulcers are sterile and develop on extensor surfaces of limbs[15].

There are 4 PG varieties: ulcerative, pustular, bullous and vegetative PG[28]. Ulcerative PG is a deep, painful ulcer with necrotic, purulent center and undermined edges (Figs. 2 A and B). Pustular PG is a sterile, painful pustule that doesn't become ulcerated. Bullous PG begins as tense bullae that quickly progress into an ulcer. Vegetative PG is a superficial ulcer that slowly turns into an exophytic lesion[18] (Figs. 3 A and B). Of these, the ulcerative and the pustular varieties are the most associated with IBD[28]. Most frequent localizations are tibial and peristomal in patients with colostomy[29]. The pathergy phenomenon occurs in 30% of cases, which represents an exaggerated response to a skin lesion (trauma)[19]. PG originating from erythema nodosum lesions has been reported[15].

Prevalence

It occurs mainly in CNSUC severe forms and may have a clinical evolution that is independent of the IBD status[30]. Its prevalence in these patients is 1%-2% and it occurs on average at 6.5 years of IBD onset[10,13,18].

These patients may also develop peristomal PG 2 months to 25 years post-surgery. This variety also has an evolution that is independent of the disease[5].

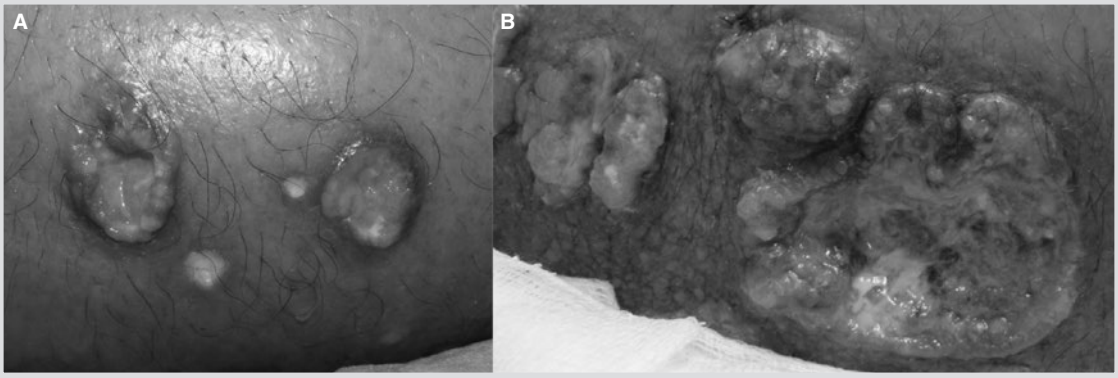

Figure 3. ***A*** *and* ***B****: Vegetative pyoderma gangrenosum.*

Table 2. Pyoderma gangrenosum diagnostic criteria

Major criteria	Minor criteria
1. Painful, necrotic ulcer with irregular and undermined violaceous edge. – 1-2 cm expansion per day or 50% size increase in 1 month. – Intense pain for the ulcer's size. – Proceeded by a papule, pustule or bulla.	1. Histopathological findings (sterile neutrophilia on dermis ± mixed inflammatory infiltrate ± lymphocytic vasculitis).
2. Other causes have been discarded. – Skin biopsy is required to rule out other differential diagnoses	2. PG-associated systemic disease (IBD, IgA-associated gammapathy, neoplasm or arthritis). 3. History suggestive of pathergy or cribriform scarring. 4. Rapid response to systemic steroids (1-2 mg/kg/day with 50% size decrease at one month).

2 major and 2 minor have to be met[31].

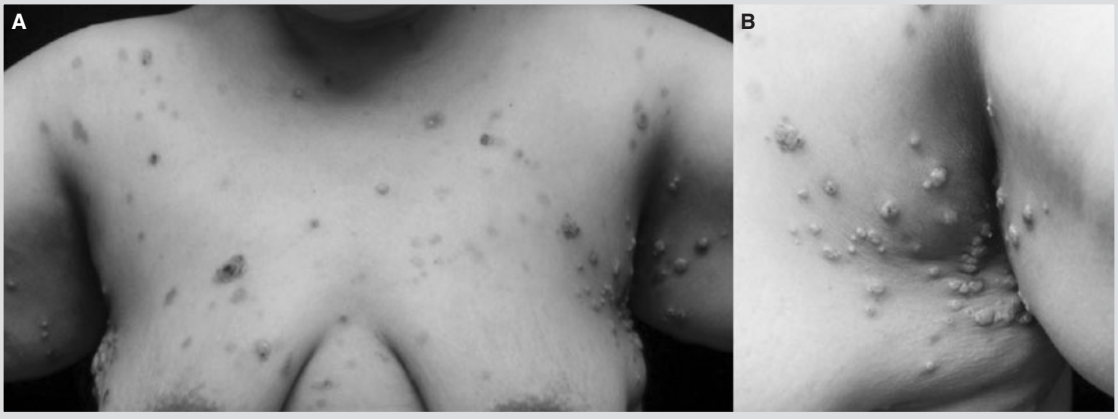

Figure 4. ***A*** *and* ***B****: Pyodermatitis vegetans.*

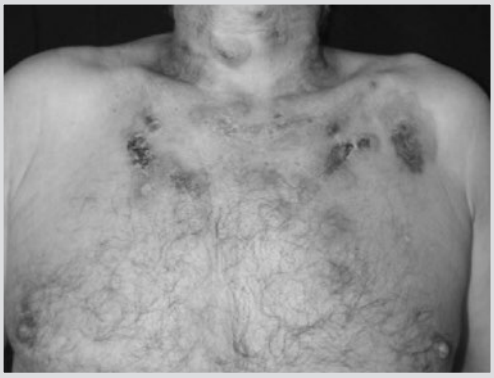

Figure 5. *Sweet's syndrome.*

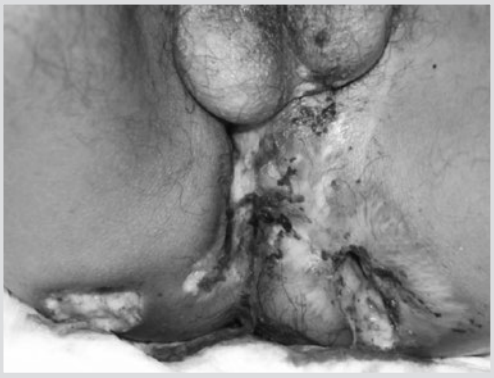

Figure 6. *Fissures, ulcers and fistulae.*

It is an exclusion diagnosis for which the diagnostic criteria shown in table 2 were developed.

Treatment

Improvement does not always occur with IBD treatment and the response to intestinal surgical resection is unpredictable[32]. If the PG is localized, topical therapy with steroids, tacrolimus, intralesional steroids (triamcinolone acetonide 10-40 mg/dl) can be initiated[14,33,34]. Systemic steroids are given at 0.5 to 2 mg/kg/day or cyclosporine at 2-5 mg/kg/day doses[34]. Within the first 24-72 hours of treatment there is pain and erythema reduction, which indicates good response[31]. In patients with treatment-refractory PG, infliximab has been successfully used since the first administration at 5 mg/kg/2 weeks[23,35]. Infliximab has the fastest response and is the most widely studied biological agent[5].

Pyodermatitis vegetans and pyostomatitis vegetans

Pyodermatitis vegetans is a rare manifestation of IBD that occurs mainly in patients with CNSUC[10,18]. It occurs mainly in axillary or inguinal folds, but it can also be present on the trunk and extremities[10]. These lesions are characterized by vegetative exophytic pustules and plaques, the rupture of which causes foul-smelling erosions[16] (Fig. 4).

Pyostomatitis vegetans is a rare manifestation that involves labial, gingival and oral mucosa[36]. These lesions are multiple, friable pustules that produce hemorrhagic ulcerations and erosions, which can involve any part of the oral cavity (labial, gingival and oral mucosa)[5]. It is observed mainly in 34-year old males[37]. In the chronic variant there are fissures resembling a "snail track", in addition to cobblestone appearance[14].

The pathogenesis of both entities is unknown, but it is thought to be due to abnormal immune responses[10]. In patients with these manifestations, in-depth studies have to be carried out in order to rule out the presence of IBD[36]. Both manifestations follow the course of the bowel disease, are IBD specific markers and occur mainly in CNSUC[11,28].

Treatment

High-dose systemic steroids are effective and are regarded as the management of choice for pyostomatitis vegetans[14,18]. Antiseptic mouthwashes and topical steroids are used for topical treatment[5]. There are frequent recurrences, especially when systemic steroids are reduced[37]. Second-line options include sulphasalazine, dapsone, azathioprine and cyclosporine[18]. In cases of CNSUC, colectomy has demonstrated pyostomatitis vegetans remission in several cases[15].

Sweet's syndrome (SS)

SS clinical manifestations are erythematous plaques or nodules on the face, neck and limbs that are accompanied by fever and leukocytosis[13] (Fig. 5). These lesions are tender and non-pruritic in nature[38]. This neutrophilic dermatosis is accompanied by fever and peripheral neutrophilia with > 70% neutrophils[16].

It is more common in women with disease activity[39]. Forty cases have been reported in the literature and it occurs especially in patients with CNSUC[10,40]. There

Table 3. Nutritional deficiencies

Deficiency	Skin manifestations	Treatment
Essential fatty acids	Unspecific eczema and xerosis[14].	Dietary supplementation.
Amino acids and proteins	Nail plate and hair alterations[16].	Dietary supplementation.
Vitamin B3 (niacin)	The classic tetrad: Dermatitis, diarrhea, dementia and death. Mucosae: Cheilitis, glossitis, angular stomatitis[5]. Photosensitive, bilateral, symmetric, polymorphous dermatosis, characterized by well-defined burning, edematous pruritic erythema with Casal necklace, and glove-and-stocking distribution. Subsequently, it becomes fixed, hyperpigmented and hyperkeratotic, affecting bony prominences as well[50].	500 mg of nicotinamide or nicotinic acid daily for several weeks[5].
B complex	Stomatitis, cheilitis and angular glossitis[16].	10 mg riboflavin, 100 mg pyridoxine, 5 mg folic acid per day. 1 mg cyanocobolamine per week[5].
Vitamin C (Scurvy)	Alopecia, gingival bleeding, hyperkeratotic papules, corkscrew hair, lower limbs perifollicular hemorrhage[50].	100-300 mg ascorbic acid[5].
Vitamin K	Purpura[16].	5-10 mg IM phytonadione[5].
Zinc (Acrodermatitis enteropathica)	Most common deficiency in IBD[10]. Periorificial and acral psoriasiform erythema. It is accompanied by chronic paronychia, nail plate dystrophy, diffuse alopecia (telogen effluvium), mucositis and candidiasis[50].	Zinc sulfate 220 mg PO[10].

may be also pulmonary (chronic cough) and ocular (conjunctivitis, episcleritis, keratitis) involvement[18].

Skin biopsy is helpful to differentiate it from erythema nodosum by neutrophilic infiltrates found when it affects the lower limbs[41].

Treatment

This condition can persist for long periods of time if left untreated[18]. The lesions respond to an increase in immunosuppressant intensity[40]. If the disease is localized, topical steroids are started; if the condition is severe, prednisone 40-80 mg/day can be initiated[19]. Colchicine and potassium iodide are useful as second-line[10]. The lesions do not leave scars when healed[11,15].

Granulomatous dermatoses

Perianal disease: Fissures, fistulae and abscesses

In Crohn's disease, the spectrum of the disease encompasses from perianal erythema, aphthous ulcers to perianal fistulae[13]. These lesions occur due to involvement of skin and mucosa via a mechanism that is similar to that occurring at the gastrointestinal level[17]. Perianal disease is usually Crohn's disease first manifestation, and fissures are observed in 21%-35% of patients[13,42].

Anal fissures resemble idiopathic fissures except that they are not found at the posterior midline of the anus. In multiple fissures not responding to treatment or found at atypical places, Crohn's disease, neoplasm or infection should be suspected[43] (Fig. 6).

There are also entero-cutaneous fistulae at the laparotomy and umbilical scars.

Perirectal fistulae and abscesses can be adequately assessed by means of magnetic resonance imaging, endoscopic ultrasound and exploration under anesthesia[44,45].

Treatment

Management of fissures can be carried out with stool softeners, sitz baths and nitroglycerine ointments (0.2-0.4%) or calcium channel blockers[43].

Optimal management of fistulae secondary to IBD is accomplished with surgical approach (setons, fistulotomy)[25]. Infliximab administration at a 5 mg/kg body weight on weeks 0, 2, 6 and then every 8 weeks is

Table 4. Skin manifestations secondary to medications

Medication	Secondary dermatoses
Anti-TNF	Granuloma annulare, drug-reaction dermatitis, leukocytoclastic vasculitis, SLE, psoriasis, eczematous lesions, squamous cell carcinoma or T or B cell lymphoma[10,16,51].
Azathioprine	Drug-reaction dermatitis, hives, angioedema, pruritus or squamous cell carcinoma[16,52].
Cyclosporine	Gingival hyperplasia, acne, viral warts, sebaceous hyperplasia, purpura, leukocytoclastic vasculitis, squamous cell carcinoma or lymphoma[16,25].
Steroids	Skin infection, acneiform reaction, atrophy, telangiectasias, striae, fat redistribution or hypertrichosis[10,16,25].
6-mercaptopurine	Alopecia, skin and nails hyperpigmentation, oral mucosa ulcers or squamous cell carcinoma[16,52].
Methotrexate	Oral mucosa and skin ulcers, toxic epidermal necrolysis (TEN), onycholysis, phototoxicity, pseudolymphoma or squamous cell carcinoma[16].
Sulfasalazine/Mesalazine/ Sulfapyridine	Lichen planus, hives, vasculitis[16].

considered first-line for patients with fistulae and perianal Crohn's disease[46,47].

Oral Crohn's disease

It occurs in 8%-9% of cases and is considered an extension of the granulomatous disease of patients with Crohn's. There is painful edema of the lips, mucosa and gums, as well as ulcers and nodules. The mucosa and gums cobbled appearance resembles the intestinal lesions[25].

Metastatic Crohn´s disease

It manifests itself as papules, nodules and plaques with non-caseating granulomas on the limbs or anogenital region[25,48]. These lesions are difficult to identify, and when they occur, Crohn's patients usually have distal colonic involvement[48]. These lesions often respond to the treatment more slowly than intestinal lesions[48]. The combination of metronidazole and systemic steroids has been successfully used[49].

Secondary dermatoses

Undernourishment

The factors involved are: poor food intake, poor digestion and absorption, bacterial overgrowth, surgical resection, colonic losses, due to metabolic demand or treatment-related. Essential fatty acid, zinc and iron deficiency is mainly observed in patients with CNSUC[10]. These deficiencies improve when supplemented[18] (Table 3) (Fig. 6).

Drug-induced side effects

In spite of receiving treatment, patients with IBD can experience dermatoses suggestive of activity or as a drug-induced side effect. In addition, certain medications are associated with dermatosis due to nutritional deficiencies (sulfapyridine, folic acid; azathioprine, niacin; and cholestiramine, liposoluble vitamins). Most widely used medications and their respective dermatological adverse effects are identified in table 4[10,18].

Conclusions

IBD, with its two components, CNSUC and Crohn's disease, has multiple extraintestinal manifestations, out of which dermatological manifestations are common and can be helpful in not-yet-diagnosed cases, hence their high relevance.

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