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# Metastatic cutaneous Crohn's disease as an important differential diagnosis of granulomatous skin disease

## *Doença de Crohn metastática cutânea como importante diagnóstico diferencial de doença granulomatosa em pele*

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### ABSTRACT

Patients with Crohn's disease may show extraintestinal manifestations, including cutaneous, whose frequency ranges from 2% to 34%. Metastatic cutaneous Crohn's disease is considered a specific and rare manifestation, since the histopathology reveals granulomatous pattern with the same characteristics of the underlying bowel condition. The objective of this study is to report two cases of metastatic cutaneous Crohn's disease confirmed by histopathologic analysis, after excluding other granulomatous skin diseases. Case 1: Adult woman with pruritic erythematous scaly plaques disseminated on the upper limbs. Case 2: Adult man with grayish hyperchromic plaque infiltrated on the left buttock.

**Key words:** Crohn disease; skin; granuloma.

### INTRODUCTION

Inflammatory bowel disease is an idiopathic and inflammatory condition of the intestinal tract, represented by Crohn's disease and ulcerative colitis. Crohn's disease may result in changes from the mouth to the anus, with no continuous lesions (in most cases start in the terminal ileum), affecting the full-thickness (transmural) of the intestinal wall<sup>(1)</sup>. The prevalence of extraintestinal manifestations in inflammatory bowel diseases ranges from 25% to 40%, and the skin involvement is present in 2% to 34% of patients<sup>(2)</sup>.

Among the cutaneous manifestations, the metastatic Crohn's disease is considered an uncommon manifestation of the disease, as it is characterized by granulomatous skin lesions with the same histological characteristics of the underlying bowel disease<sup>(3)</sup>. Its pathogenesis is not well understood. It is believed that bacterial translocation through the intestinal barrier trigger adaptive immune response unable to discriminate between microbial and skin epitopes. Therefore, the sick gastrointestinal mucosa would cause immune response in the extraintestinal environment, such as the skin, through epitopes common to the bowel and

the skin. The T cells of the intestinal mucosa are important for maintaining homeostasis, defined as the balance between the mucosal epithelium, intestinal microbes and the host immune response. Abnormal T cell response to microbial antigens may disturb this balance, causing chronic inflammation and excessive release of cytokines, resulting in inflammatory bowel disease. The cutaneous manifestations could therefore be explained by the T cells of the intestinal mucosa that, in an aberrant way, move to the skin becoming exposed to cutaneous antigens and, ultimately, causing skin changes. Inflammatory bowel disease should be considered a systemic disease not limited to the gastrointestinal tract, since many patients develop extraintestinal symptoms, such as cutaneous, with potential detrimental impact on the functional status and quality of life of the patient<sup>(4)</sup>.

### CASES REPORT

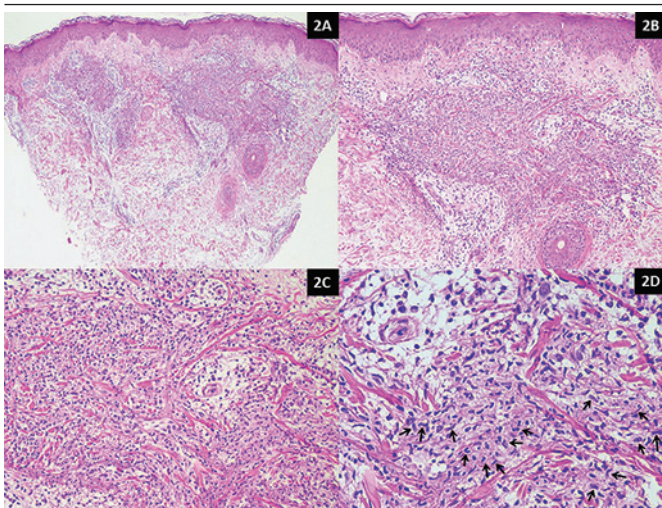
#### Case 1

Woman, 39 years old, with perianal Crohn's disease for 12 years with history of fistulotomy, colectomy and proctocolectomy,

taking sulfasalazine, azathioprine and infliximab for three years and C-reactive protein (CRP) 12.5 mg/dl, without other comorbidities, sought the Dermatology service due to lesions on the upper limbs with a month of evolution. Dermatological exam showed: erythematous scaly plaques disseminated on the upper limbs (**Figure 1**). Biopsy of the cutaneous lesions on upper limb showed chronic granulomatous dermatitis of interstitial pattern (**Figura 2**). Stains for fungi and mycobacteria research (periodic acid-Schiff [PAS]-cd and Fite Faraco, respectively) showed no microorganisms. The condition was interpreted as



**FIGURE 1** – Clinical aspect of patient with metastatic cutaneous Crohn's disease: erythematous scaly plates in left arm



**FIGURE 2** – 2A) photomicrograph of skin biopsy showing lymphohistiocytic inflammatory infiltrate between the connective bundles of the reticular dermis, without the presence of caseous necrosis, (HE, 20 $\times$ ); 2B) reticular dermis with lymphohistiocytic infiltrate (HE, 40 $\times$ ); 2C) detail to lymphohistiocytic infiltrate between the dermal connective bundles, without caseous necrosis (HE, 100 $\times$ ); 2D) the arrows indicate some epithelioid histiocytes (HE, 400 $\times$ )

HE: hematoxylin and eosin.

metastatic cutaneous Crohn's disease. We chose to maintenance infliximab and increase azathioprine dosing, and observed improvement in the lesions after four months.

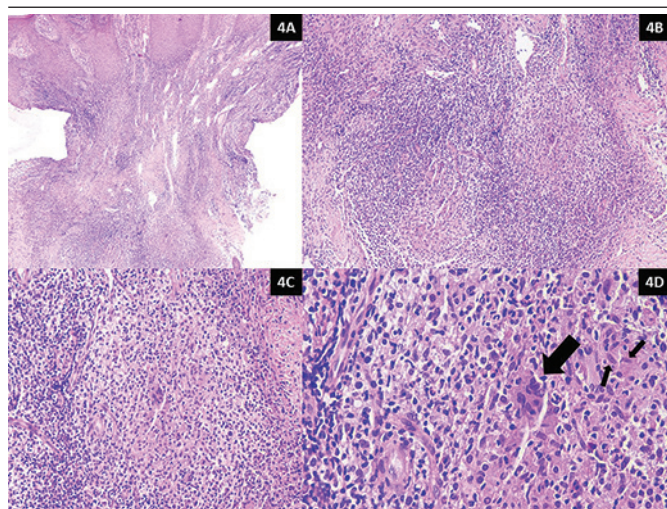
## Case 2

Man, 29 years old, with Crohn's disease in the terminal ileum for 12 years, taking azathioprine since diagnosis, current CRP 3.19 mg/dl, with no other comorbidities, attended the same service due to asymptomatic lesion on the buttock for six months. Dermatological exam showed: grayish hyperchromic plaque, 6  $\times$  7 cm, infiltrated on the left buttock, not adjacent to the anus (**Figure 3**). Skin biopsy of the area showed marked epidermal hyperplasia and granulomatous inflammatory pattern in the dermis (**Figure 4**). Stains for fungi and mycobacteria research (PAS-cd and Fite Faraco, respectively) showed no microorganisms. He denied systemic symptoms, injection site or previous vaccination. Negative result in research for infectious granulomatous diseases. We opted for treatment with topical corticotherapy.



**FIGURE 3** – Clinical aspect of patient with metastatic cutaneous Crohn's disease: grayish infiltrated plate on the left buttock, not adjacent to the anus





**FIGURE 4** — 4A) photomicrograph of skin biopsy that shows marked reactive epidermal hyperplasia and dense lymphohistiocytic inflammatory infiltrate between the connective bundles of the reticular dermis, with granuloma formation, without caseous necrosis (HE, 20×); 4B) granuloma in the dermis, without caseous necrosis (HE, 40×); 4C) on detail granuloma in the dermis, without caseous necrosis (HE, 100×); 4D) the small arrows indicate some epithelioid histiocytes and the largest arrow points a multinucleated giant cell (HE, 400×)

HE: hematoxylin and eosin.

## DISCUSSION

Cutaneous manifestations directly related to inflammatory process of Crohn's disease in the intestine include metastatic Crohn's disease, perianal and peristomal ulcers, fistulas and oral granulomatous changes<sup>(5)</sup>. The extraintestinal manifestations in patients with Crohn's disease are most frequently observed in individuals with human leukocyte antigen (HLA)-A2, HLA-DR1 and HLA-DQw5<sup>(6)</sup>.

Metastatic Crohn's disease, or cutaneous at a distance, is highly infrequent, although this just is based on series of isolated cases. By definition, these are non-caseating granulomatous cutaneous lesions, which are not contiguous with the intestinal Crohn's disease.

It is well recognized in adults and extremely rare in children. Clear correlation between the activity of intestinal and metastatic disease was not found. It can develop simultaneously or precede the gastrointestinal involvement<sup>(7)</sup>. Clinically, patients present plaques, nodules and erythematous to purplish ulcers, predominantly in skin of edges and folds. Face and genitals are less affected<sup>(8)</sup>.

The heterogeneity of its manifestation and clinical course, as seen in the cases reported may delay diagnosis, which is based on clinical evaluation and skin biopsies in the context of a patient with Crohn's disease. In the cases presented, lymphohistiocytic inflammatory infiltrate between the connective bundles of the reticular dermis was evidenced by histopathological evaluation, one of them with granuloma formation without the presence of caseous necrosis or foreign bodies; staining for detection of mycobacteria and fungi showed no microorganisms, allowing to diagnose metastatic Crohn's disease, therefore exclusion of other granulomatous diseases of the skin. In metastatic Crohn's disease, histological study reveals non-caseating granuloma, and other granulomatous dermatoses should be discarded. Caseous necrosis absence helps to distinguish with lupus vulgaris, and more dense lymphocytic collection is more common in metastatic Crohn's disease than in sarcoidosis. Other differential diagnoses include pyoderma gangrenosum, erythema nodosum, Sweet's syndrome, yeast infections and mycobacterial infections, foreign body reactions, hidradenitis suppurativa, syphilis and granulomas related to exposure to beryllium and zirconium<sup>(9,10)</sup>.

The two cases presented reveal rarity of this cutaneous manifestation: from over three hundred patients from the Clinic of Inflammatory Bowel Diseases of the Clinical Hospital of the Universidade Federal do Paraná, between April and September 2015, those reported here were the only ones with such a manifestation with prevalence lower than 1% in this group of patients. Therefore, we emphasize the importance of diagnostic suspicion of the patients affected by Crohn's disease with cutaneous lesions, often asymptomatic and heterogeneous, and histopathologic evaluation and exclusion of other granulomatous conditions are essential to confirm the diagnosis, allowing early treatment.

## RESUMO

*Pacientes portadores de doença de Crohn podem apresentar manifestações extraintestinais, inclusive cutâneas, cuja frequência varia de 2% a 34%. A doença de Crohn metastática cutânea é considerada manifestação específica e rara, visto que apresenta à histopatologia padrão granulomatoso com as mesmas características da condição intestinal subjacente. O objetivo deste estudo é relatar dois casos de doença de Crohn metastática cutânea confirmados por análise histopatológica, após exclusão de outras doenças granulomatosas da pele. Caso 1: Mulher adulta com placas eritematodescamativas pruriginosas disseminadas em membros superiores. Caso 2: Homem adulto com placa hipercrômica acinzentada e infiltrada em nádega esquerda.*

**Unitermos:** doença de Crohn; pele; granuloma.

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