Metastatic Crohn's disease despite infliximab therapy*

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Abstract: Metastatic Crohn's disease is a rare extraintestinal manifestation of Crohn's disease. It is characterized by polymorphic skin lesions formed by non-caseating granulomas located on anatomical sites distant from the gastrointestinal tract. We report a rare case of metastatic Crohn's disease, simultaneously displaying multiple clinically heterogeneous cutaneous lesions, in a patient with previously diagnosed Crohn's disease in remission due to anti-TNF-α use. This case highlights the need for high clinical suspicion and early biopsy in the setting of a patient with Crohn's disease and persistent skin lesions, even under biologic therapy. Furthermore, it reinforces the need of monitoring of the serum level of infliximab, increasing the dose in case it is low or undetectable.

Keywords: Biological agents; Crohn's disease; Granuloma

INTRODUCTION

Metastatic Crohn's disease (MCD) is a rare extraintestinal manifestation of Crohn's disease (CD), characterized by polymorphic cutaneous lesions formed by non-caseating granulomas localized in anatomical sites distant form the gastrointestinal tract.

We report a rare case of MCD with a generalized distribution and predilection for skin folds, in a patient with stable CD under treatment with infliximab.

CASE REPORT

A 36-year-old female patient presented to the clinic with erythematous, erosive and painful plaques on the perioral, perinasal, post-auricular and occipital regions (Figure 1). She also had ill-defined, erythematous, scaly plaques on the trunk, axillae, buttocks, and inguinal region (Figure 2). In addition, there was obvious edema of the vulva and mons pubis (Figure 3).

Ileocecal CD was diagnosed 10 years prior and was in remission under treatment with azathioprine (2mg/kg/**day)** and infliximab (5 mg/kg every eight weeks). The patient noticed improvement of the erythematous, erosive lesions in the first few days of infliximab use, but worsening in between infusions. On the other hand, the scaly plaques on the trunk and buttocks worsened after infliximab. Suspecting MCD (on the skin folds and vulva) and also paradoxical psoriasiform reaction to infliximab, (trunk and buttocks), we performed two biopsies — one of the erosive plaque on the post-auricular region and another of the scaly lumbar lesion. Surprisingly, both lesions revealed a granulomatous infiltrate of lymphocytes, epithelioid histiocytes, plasma cells, some eosinophils and multinucleated giant cells occupying the dermis (Figure 4). Mycobacterial, bacterial, and fungal culture was negative. These findings were consistent with MCD, with no evidence of paradoxical psoriasiform reaction to infliximab.

The patient started treatment with metronidazole (500 mg orally every 8 hours) and topical steroids, with partial improvement. Because of the persisting lesions, we opted to dose the serum

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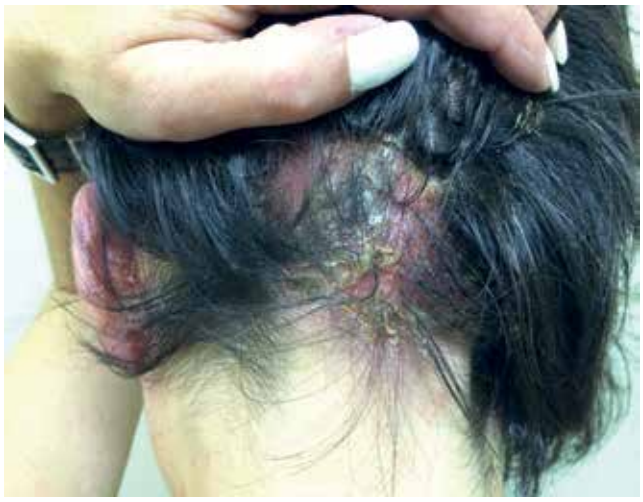

Figure 1: Erythematous, erosive, crusty and painful plaques on the occipital and post-auricular regions

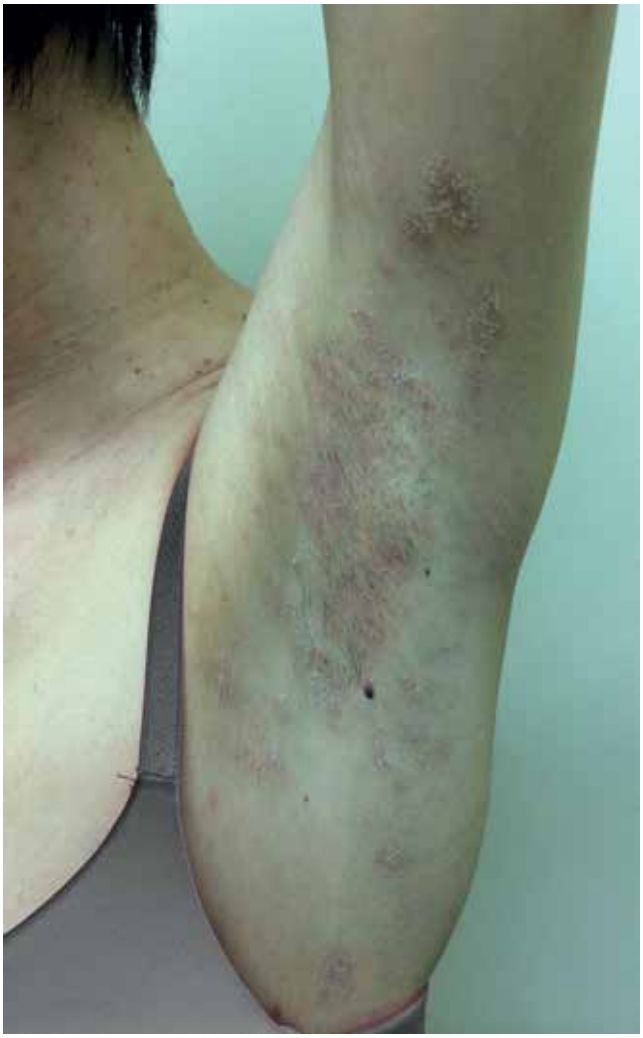

Figure 2: iII-defined scaly plaques on the left axilla

level of infliximab and antibodies against anti-TNF-α: the level was low (0.7 µg/mL) and no antibodies were seen. The interval between infliximab infusions was reduced to six weeks, with clinical improvement 12 weeks after adjusting the dose.

DISCUSSION

CD is a chronic, inflammatory and granulomatous intestinal disease that, along with the typical gastrointestinal involvement, can also present with extraintestinal manifestations. Dermatological findings occur in 44% of patients and MCD is a rare variant of these manifestations (less than 100 cases reported in the literature). It is characterized by non-caseating granulomas in anatomical sites distant to the gastrointestinal tract, but its pathophysiology is not completely understood. The possibility of antigens or immune complexes from the tract lodging in the skin, leading to perivasculitis, has been suggested.[1,2] Other authors support the theory of crossed reactivity among antigens from the gastrointestinal tract and skin.[3]

MCD usually presents in patients with a previous history of CD; however, there is no correlation with the intestinal activity of CD.[2] Both genders are equally affected, and the age at diagnosis varies between 29 and 39 years.[4]

Clinically, the lesions can be solitary or multiple, with or without associated pain.[4,5] On the genital region, they can present with diffuse erythema, edema and fissures, whereas on other parts of the skin erythematous-violaceous plaques or nodules are more frequent.[6] Rarely, lichenoid papules, pustules or abscesses with fistulous drainage can be the first manifestation of MCD. Areas frequently affected include intertriginous and flexural regions, trunk, upper limbs and face.[5,7]

MCD histology is characterized by the presence of sterile, non-caseating, epithelioid granulomas in the superficial and deep dermis, with the differential diagnosis of sarcoid granulomas.[1]

MCD treatment has only been described in case reports, what can be explained by the rarity of this condition. Metronidazole and corticotherapy (topical or systemic) have been used, besides anti-TNF-α agents in more severe or refractory situations.[8] However,

Figure 3: Edema of the vulva and mons pubis, followed by ill-defined erythema and scaling

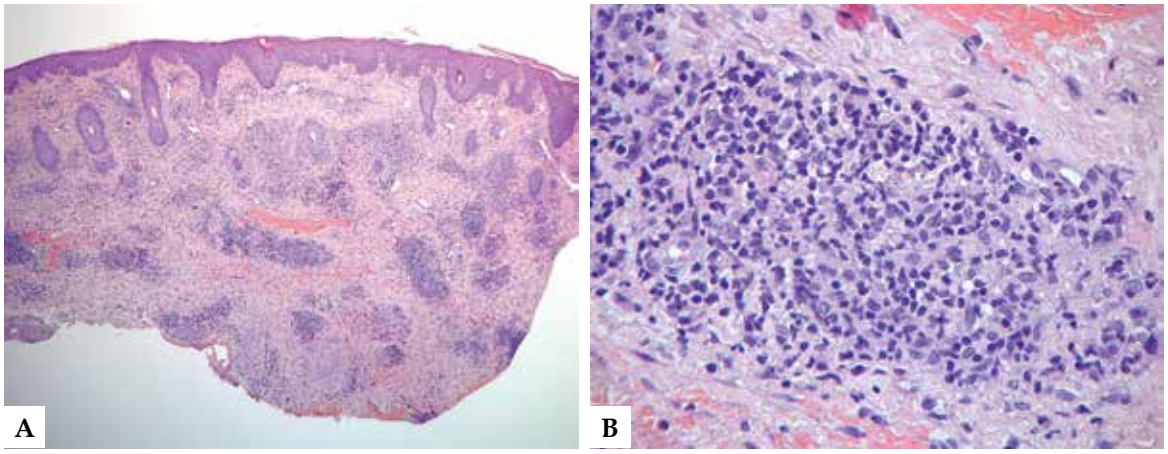

Figure 4: A. The histology of the post-auricular lesion reveals granulomatous infiltration occupying the whole dermis. There is mild focal parakeratosis, acanthosis and spongiosis of the overlying epidermis (Hematoxylin & eosin, X40).
B. iII-defined granuloma with histiocytes, some multinucleated giant cells, lymphocytes and plasma cells (Hematoxylin & eosin, X200)

in the case reported, the patient developed lesions while being treated with infliximab. Despite the report of cases of psoriasiform lesions in patients treated with anti-TNF-α, the skin biopsy ruled out this paradoxical condition.[9] Therefore, we speculated that the serum level of infliximab was low, or that antibodies could have been formed, what would potentially reduce therapeutic efficacy. Serum levels higher than 2.79μg/ml have been associated with gastrointestinal remission, and there is a correlation between serum level of infliximab and clinical remission with mucosal regeneration.[10] In the reported case, serum levels of infliximab were low (although there was no evidence of antibodies anti-infliximab), and the shortening of the interval between doses provided added clinical improvement.

This is an uncommon case of MCD, with heterogenous lesions affecting multiple anatomical sites, some of them rare, such as the vulva, in a patient with stable CD treated with infliximab.[6]

Monitoring of serum levels of infliximab should be considered in face of the suspicion of loss of therapeutic efficacy and can result in dose increase when the levels are low/undetectable, with potential clinical improvement. ❑

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