ABSTRACT

Introduction: Metastatic Crohn’s disease (MCD) is an extraintestinal manifestation of Crohn’s disease, with biopsy as fundamental diagnostic tool. There are few references to MCD in children, with a 0.5-1% estimated incidence in adults. There is no consensus about its therapeutic approach. We describe our diagnostic and therapeutic experience in MCD.

Case reports: Four cases of MCD are described in our Pediatric Gastroenterology Unit in a tertiary care hospital. The age at diagnosis was between 7 and 13 years. Lesions appeared before the diagnosis of Crohn’s disease in three of them, and during the course of the disease in another one, with genital location in three patients and bilateral pretibial region in the other. All four cases demonstrated non-caseificant granulomas on biopsy. Only two patients used exclusive enteral nutrition therapy with complete resolution, while other two cases received a combination of therapies (corticosteroids, azathioprine, tacrolimus, infliximab and adalimumab) because of recurrence. Only one case required surgery after poor clinical control.

Discussion: The MCD is infrequent but must always be included in the differential diagnosis of cutaneous lesions in Crohn’s disease, considering it could be the debut of the disease. We will rely on biopsy anyway for definitive diagnosis. In this series the genital region is verified as the most commonly affected in children. The therapeutic approach does not differ from the management of intestinal involvement.


INTRODUCTION

Inflammatory bowel disease (IBD) should be considered as a multisystemic disease, since it may affect practically any organ in the body. Extraintestinal manifestations (EIM) may appear at the time of diagnosis, before or after it (Table I), with a lower prevalence in pediatric patients than in adults, about 24-28% along the evolution (1,2). Mucocutaneous involvement is the second most common one after bone and joint, with a prevalence of approximate-
improvement. After being with this triple therapy for 1 year, he developed edema and skin redness in penis and scrotal sacs. The patient continued topical treatment with steroids and antibiotics, without improvement. He denied fever, anorexia, abdominal pain or diarrhea, and perianal lesions remained stable. On physical examination important scrotal and penis edema, with erythema, nodules with no ulcer, slightly tender to palpation, was observed (Fig. 2). Testicular

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**Table I. Extraintestinal manifestations in inflammatory bowel disease**

<table>
<thead>
<tr>
<th>Reactive/non specific</th>
<th>Aphthous stomatitis</th>
<th>Erythema nodosum</th>
<th>Gangrenous pyoderma</th>
<th>Sweet syndrome</th>
<th>Cutaneous vasculitis</th>
<th>Granulomatous cheilitis</th>
<th>IgA dermatosis</th>
<th>Epidermolysis bullosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific/granulomatous</td>
<td>Direct extension</td>
<td>Perianal</td>
<td>Peristomal</td>
<td>Perifistular</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Autoimmune cutaneous diseases</td>
<td>Psoriasis</td>
<td>Sistemic eritematos lupus</td>
<td>Scleroderma</td>
<td>Alopecia</td>
<td></td>
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<tr>
<td>Secondary to nutritional deficiencies</td>
<td>Enteropatic acrodermatitis (zinc)</td>
<td>Pelagra (nicotinic acid/niacin)</td>
<td>Hair and nail dystrophy (biotin)</td>
<td></td>
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<tr>
<td>Secondary to medical treatment</td>
<td>Acne and striae</td>
<td>Erythema multiforme</td>
<td>Peristomal dermatitis</td>
<td>Drug-induced lupus</td>
<td>Hypertrichosis</td>
<td>Alopecia</td>
<td></td>
<td></td>
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</tbody>
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Modified from: Romero M et al. (8)

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Fig. 1. HE 200X. MCD histological lesions in vulvar case 1. Necrotizing granulomatous vasculitis with features compatible with Crohn’s disease.

Fig. 2. Genital lesion in penis and scrotum in case 2.
ultrasonography showed thickening of the scrotum, with significant increase in blood flow. The testes were normal with adequate intratesticular flow. Scrotal skin biopsy resulted in noncaseating granulomatous inflammation. Cultures and special staining techniques (Zielh and PAS) were negative. The basic treatment was modified, increasing the dose of prednisone and associating metronidazole. There was a marked improvement of genital lesions, but several months after reducing the dose of systemic steroid the genital skin lesion worsened and it was decided to start infliximab (only induction under the scheme 0, 2, 6 months), obtaining partial response but failing to remove the corticosteroid treatment. The patient, after 6 months, developed fever, bloody diarrhea, abdominal pain and worsening of genital injury, so tacrolimus was associated (dose of 0.12 mg/kg/day, adjusted for 5-10 ng/mL blood levels). Two months later, prednisone could be retired with good clinical response but genital injury persisted without full resolution after several months. Ileocolic resection surgery was carried out with ileostomy discharge, thereby achieving very good development of genital injury, with complete disappearance.

Case 3

Thirteen-year-old female patient was referred from the Endocrinology consultation because of stunting and abdominal pain for 3 years. She suffered from low intensity recurrent abdominal pain and mucous and bloody inconsistent stools in the previous two weeks. The examination revealed tenderness in the right lower quadrant, painful swelling with inflammatory signs in vulvar and anal fissure as well as increased CRP, ESR and fecal calprotectin. Enteromagnetic resonance was performed, discarding the presence of any contiguity or fistulous lesion between vulvar lesion and the gastrointestinal tract. Endoscopy showed moderate ileocolonic involvement. With the diagnosis of CD (A1bL3B1G0) she started exclusive nutritional treatment for 8 weeks, mesalazine and metronidazole with good clinical response and progressive decrease in vulvar lesion, achieving complete resolution.

Case 4

A 7 year-old boy was referred to our Gastroenterology unit because of recurrent abdominal pain and purple skin lesions in the front face of both tibias (Fig. 3), suggestive of erythema nodosum. Analytical data evidenced systemic inflammation (CRP 20 mg/L, ESR 40 mm/1st h, fecal calprotectin 400 mcg/g) and he was diagnosed of CD (A1aL-3B1G0), with presence of deep ulcers and granulomas in endoscopy. After diagnosis, he started with exclusive enteral nutrition for 8 weeks and azathioprine, with obvious improvement in clinical and skin lesions. After nutritional therapy ended, painful bilateral pretibial edema reappeared, with suspicion of erythema nodosum, starting systemic steroids at doses of 1 mg/kg/day and achieving complete resolution, but with reappearance when attempting to decrease prednisone. Thereby, biopsy of the cutaneous lesions was performed, showing noncaseating granulomas compatible with MCD. Given the corticosteroid dependence, despite thiopurine therapy, and fecal calprotectin levels < 250 mcg/g, it was decided to start adalimumab (80/40/40), achieving good response with withdrawal of steroids and finally azathioprine after 12 months of combined therapy, remaining with no skin damage so far.

DISCUSSION

Ten to twenty per cent of patients with IBD have skin EIM in the course of the disease which may be of several types (Table II). Metastatic skin lesions are one of the rarest forms of skin involvement in CD patients. The MCD was first described by Park et al. in 1965, in a 70-year-old patient who was suffering from CD for four years (3). Due to the unusual presentation (there are fewer than 200 cases reported in the literature, mostly in adults), there are isolated cases, with no large series, making it difficult to draw conclusions on epidemiology (prevalence, predictors, etc.), pathogenesis, relationship with intestinal disease activity and location, and about which are the most effective treatments against it. Some revisions on this issue are Palamaras et al. (6), which include adult and pediatric patients; Keiler et al. (7), which include children aged less than 18, and Romero et al. (8), including only adults. The latter describes a prevalence of 0.66% over the course of the disease. During the period 1990-2014, 99 patients have been diagnosed with CD in our unit, with only 4 cases of MCD (4%). The age at diagnosis is 7 to 13 years with an equal gender distribution.

The pathogenesis remains unknown. For some authors it is the result of deposit of circulating immune complexes; others suggest a type IV mediated reaction between...
unknown antigens of the skin and T-lymphocytes. According to this hypothesis, *Mycobacterium paratuberculosis* antigen could be responsible for this condition, with some studies finding DNA fragments, using PCR, in intestinal samples from patients with CD. Our series has unsuccessfully sought the presence of mycobacteria. More recent theories speak of the role of beta-2 integrins and alterations in the MLH-1 gene, responsible for the repair mechanisms of DNA (6).

Clinically, the MCD can take many forms, such as ulcers, papules, nodules, indurated plaques or crusts, usually painless, and can be located at any level of the body surface. Lesions may be single or multiple, sometimes affecting different locations simultaneously (9,10). In children, the most common presentation is swelling/induration with or without associated erythema, localized in the genital area, mainly in vulva, penis and scrotum, in 85% of cases (7), while in adults they mainly affect lower extremities. In our series, the location was pretilial in one case and genital in three children (vulva, affecting labia majora; scrotum and penis).

No relationship has been demonstrated between the MCD and the activity of the intestinal disease. Like the rest of skin lesions, the MCD is more frequently related to the location of the gastrointestinal disease in case of ileocolonic or colonic involvement (6), as in our 4 cases. However, it appears to be related to the presence of other extraintestinal manifestations, unlike what happens with erythema nodosum and arthritis. An important aspect is whether or not the MCD precedes intestinal IBD. In this way, 70-80% of cases of MCD in adult patients often appear years after diagnosis of intestinal disease, while in children 85% of patients had not yet been diagnosed with IBD when metastatic skin lesions were already present, mainly noncaseating granulomas in the pathological study, guiding the clinician to a possible CD. In our series, lesions appeared before the diagnosis of IBD in 3 cases and during the course of the disease in the other one. Indeed, in most reports on MCD in children it is a skin lesion the one that initiates the study of probable IBD, with up to 74% of patients presenting unnoticed symptoms compatible with CD, especially unspecific symptoms such as recurrent abdominal pain, diarrhea, constipation or growth retardation. More striking is that up to 78% of patients suffered from concomitant perianal disease (anal fissures, fistulae, abscesses or perianal erythema) (6,7,11).

According to several publications, there is a delay time, 9 months to 4 years, from the onset of MCD lesions until the diagnosis is made. This time might be shortened if at the time of clinical suspicion all necessary complementary explorations currently available for the diagnosis of IBD could be performed (gastroscopy, ileocolonoscopy, intestinal MRI and/or video capsule endoscopy), since many of these CD cases are pauci-symptomatic. In the initial differential diagnosis, and depending on the type and location of the damage, there are various entities such as dermatitis,
intertrigo, hidradenitis suppurativa, chronic cellulitis, erythema nodosum (as thought in our fourth case), seborheic dermatitis, erysipelas, lichenoid eruptions and various sexually transmitted diseases, being forced, in some cases, to rule out sexual abuse. Regarding the granulomatous lesion, it obliges clinicians to rule out pathologies with the same pathology, such as sarcoidosis and tuberculosis (12,13). All cases in our series demonstrated the presence of noncaseating granulomas in biopsy, with all expanded etiology being negative.

There is no consensus document for the treatment of MCD. Treatment depends on the clinical condition of the patient, severity and extent of disease because many options have been tried (6,8): topical, intralesional or systemic steroids, metronidazole, dapson, tetracycline, azathioprine, 6-mercaptopurine, sulfasalazine, tacrolimus (5), cyclosporine and infliximab (14,15). The two girls in our series were quite similar according to management and further development. Their disease was controlled with enteral nutrition and mesalazine with or without azathioprine, showing complete resolution of skin lesions as well as good control of bowel symptoms. The other two cases (with pretibial involvement and genital involvement) had a torpid evolution with relapsed after corticosteroids decrease, so it was decided to start biological therapy. In the case of genital involvement, 12 years ago, infliximab was started, but only induction was achieved with no maintenance, which might have been able to reverse the MCD, and he required further association with systemic tacrolimus because of persistent symptoms. In the case of the patient with the pretibial involvement, he responded after initiation of adalimumab, and steroids could be descended until complete withdrawal. Surgical treatment is reserved for situations of failure of medical treatment. In the evolution, surgery was performed only in one of our cases, with resection and ileostomy discharge because of endoscopically increased inflammatory activity in the intestinal tract, and the reduction of inflammatory activity was the one that cured the MCD skin lesion.

CONCLUSIONS

The MCD is a rare extraintestinal manifestation. It is usually located at the genital level in children and coincides with inflammatory bowel involvement in a high percentage of patients. The diagnosis is confirmed by demonstration of noncaseating granulomas in tissue biopsies. The therapeutic option will be chosen depending on the extent and severity of the disease, being nutritional therapy an option in milder cases of debut. Biological, used in the last 10 years, are a good way to control the MCD, but not always avoiding local surgery in severe cases. Erythema nodosum must be ruled out, as in case 4.

REFERENCES