SHORT COMMUNICATION

Chronic Granulomatous Disease as Differential Diagnosis to Crohn's Disease in Children: a Case Report

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Chronic granulomatous disease (CGD) is a rare primary immunodeficiency caused by a defect in one of the subunits of the NADPH oxidase system (1), leading to decreased macrophage capacity to eliminate bacteria and fungi. Digestive manifestations may mimic Crohn's disease (2, 3). We report a case of CGD in an 11-year-old child presenting with skin and otorhinolaryngeal manifestations, and biological and histological signs compatible with Crohn's disease.

CASE REPORT

An 11-year-old child was referred for chronic skin lesions. This child was the youngest of 6 siblings of Moroccan origin, from an intrafamilial marriage, and had neither personal nor family history of any disease. For the previous 2 years, he had presented with well-demarcated erythematous-squamous lesions of the inguinal and axillary folds (**Fig. 1**a), fissural macrocheilitis (Fig. 1b), and crusty rhinitis (Fig. 1c). The rest of the clinical examination was unremarkable, apart from dysphonia, and there were no digestive manifestations in particular. On the basis of the clinical examination, the main hypothesis was Crohn's disease. Laboratory tests showed elevated ASCA at 274 UI/mL (N < 10) with no other abnormalities. Nasal fibroscopy was normal; laryngoscopy revealed inflammation of the front third of the vocal cords. Colonoscopy was macroscopically normal. Skin and colonic biopsies revealed epithelioid granulomas with a lymphoplasmacytic infiltrate (**Fig. 2**). The diagnosis of Crohn's disease with metastatic skin involvement and contiguous otorhinolaryngeal involvement, without macroscopic digestive involvement, was retained and treatment with adalimumab was started. At 6 months after the initiation of treatment, the child was hospitalized for a febrile general condition, with *Staphylococcus aureus* liver and lung abscesses on CT scan. No improvement with adalimumab on skin manifestations was observed. In this context, an immunodeficiency test was carried out, with a positive dihydrorhodamine test and a homozygous p47(phox) mutation, leading to the definitive diagnosis of CGD.

DISCUSSION

CGD is a rare primary immunodeficiency affecting 1:200,000 births (1), with abnormality of the phagocytes (neutrophils, macrophages, monocytes, dendritic cells) caused by impairment of the NADPH system. This is responsible for deficient production of superoxide anion and other reactive oxygen intermediates, leading to recurrent infections, granulomatous complications, and premature death.

Any pathological mutation in the genes encoding the 5 subunits of the NADPH oxidase system can cause CGD (4, 5). The most common cause is a mutation in the CYBB gene ($gp91^{phox}$) located on the short arm of the X chromosome (Xp21.1-p11.4). CYBB-linked CGD is inherited in an X-linked recessive transmission, but *de novo* forms are possible. This is the predominant form in Europe, and is clinically more severe. An autosomal recessive form involving mutation of the NCF1 gene has also been described. CYBB and NCF1 mutations account for 90% of CGD cases in Europe and North America.

CGD manifestations are systemic, with pulmonary, cutaneous, lymph node, and digestive localizations in order of frequency. Patients develop both infectious and inflammatory complications. Infectious complications associated with NADPH function deficiency occur early, and their severity depends on the level of residual NADPH activity. They mainly involve bacterial infection, in particular with *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and fungal infection, in particular with *Aspergillus fumigatus* and *Candida albicans* (6). Inflammatory complications are characterized by

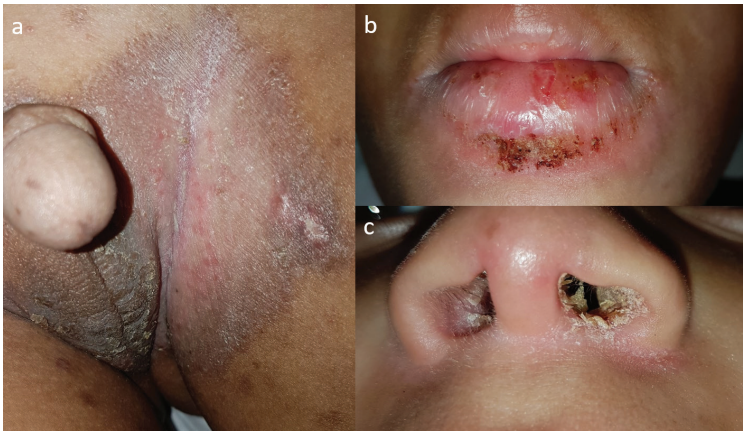

Fig. 1. (a) intertrigo of the left inguinal fold, (b) macrocheilitis, (c) crusty rhinitis. Written permission from the patient is given to publish these photos.

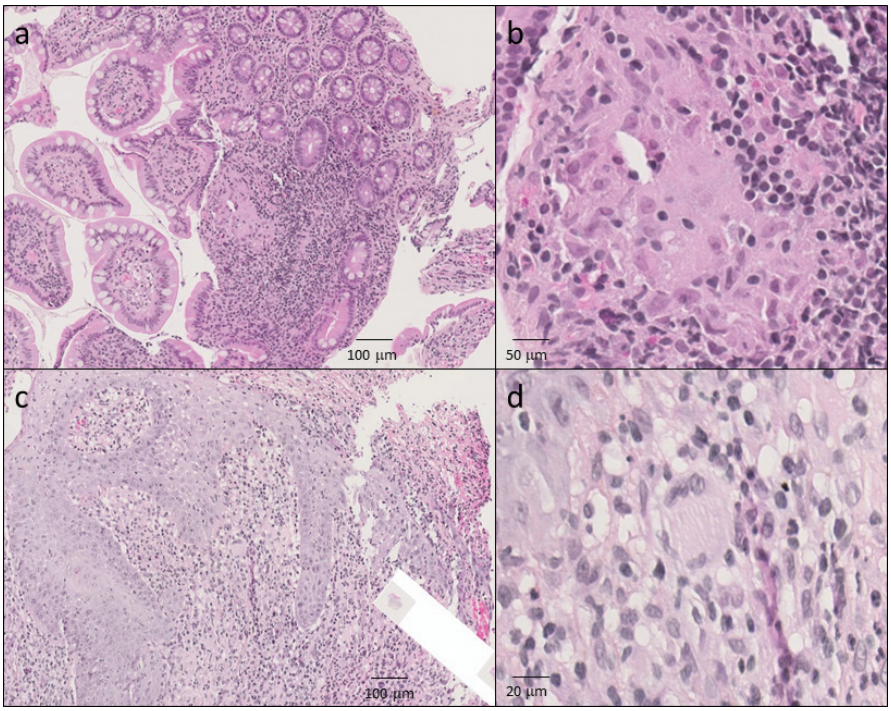

Fig. 2. Colonic biopsy revealing (a) epithelioid granulomas (HE, 4x) with (b) a lymphoplasmacytic infiltrate with swollen histiocytes containing a moderate amount of an intracytoplasmic eosinophilic and granular material (HE, 20x). (c) Macrocheilitis biopsy revealing non-caseating granuloma (HE, 4x) consisting of (d) epithelioid cells (histiocytes), lymphocytes, and plasma cells (HE, 20x).

the presence of epithelioid granulomas without caseous necrosis. Crohn's like disease is 1 of the 2 most frequent gastrointestinal manifestations in CGD. Studies show that many patients with digestive CGD localization are initially considered to have Crohn's disease. It is therefore necessary to exclude the diagnosis of CGD in any patient presenting with early-onset inflammatory disease of the digestive tract (2–4, 6). While some studies have shown that TNF blockers may improve symptoms and reduce the risk of sequelae in digestive CGD (2), they also increase the risk of infection (7). We cannot therefore exclude that the initiation of adalimumab in our patient may have precipitated the infectious complications.

CGD management is based on antibiotic and antifungal prophylaxis with trimethoprim-sulfamethoxazole and itraconazole. Allogeneic hematopoietic transplants, the only curative treatment for the disease, have also been discussed (8, 9). Earlier diagnosis and prophylactic treatments have improved patient survival rates, with a current 50% survival rate at the age of 25 (5). Our child is currently on antibiotic prophylaxis, which has not improved his skin condition.

In conclusion, we present a case of CGD in a child initially manifesting as skin signs of Crohn's disease. The onset of chronic inflammatory bowel disease at an early age, associated with infectious complications and signs of autoimmunity, should suggest the diagnosis of CGD, if possible before infectious complications.

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