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Chronic granulomatous disease as a risk factor for cutaneous lupus in childhood

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Abstract

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder that affects the phagocytic cells of the innate immune system. It is characterized by recurrent or persistent infections with granuloma formation. Lupus-like lesions have been reported in carriers of CGD and less frequently, in patients with CGD. Immunological study in these patients are usually negative. We describe the case of an 8-year-old boy with CGD who developed chronic and acute cutaneous lupus erythematous with angular cheilitis, oral ulcers, Raynaud phenomenon, and positive serologies for antinuclear, anticentromere, and anti-Saccharomyces cerevisiae antibodies.

Keywords: primary immunodeficiency; chronic granulomatous disease; lupus erythematous

Case Synopsis

An 8-year-old boy with diagnosis of X-linked GCD, chronically medicated with trimethoprim/sulfamethoxazole and itraconazole, was referred to the dermatology department for a sudden pruritic rash in sun-exposed areas. The mother also mentioned a chronic dermatosis of palms and soles, respectively, with one and six years of evolution that partially improved after the application of topical corticosteroids. The plantar lesions had been previously biopsied with suggestive signs of eczema.

On physical examination, we observe the following mucocutaneous alterations: cheilitis, oral ulcers on the tongue and buccal mucosa, erythematous macules on the soft palate, erythematous to violaceous papules and plaques symmetrically scattered over the infraorbital region, chest, back, and lateral surface of both arms, and multiple erythematous-to-violaceous, purpuric, hyperkeratotic papules and plaques on palms and heels (**Figures 1, 2**). There

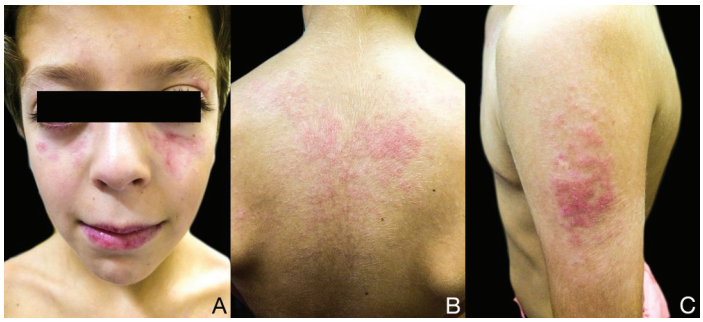

Figure 1. *Acute cutaneous lupus erythematous: erythematous to violaceous papules and plaques scattered over infraorbital region (A), back (B), and external surface of the arms (C).*

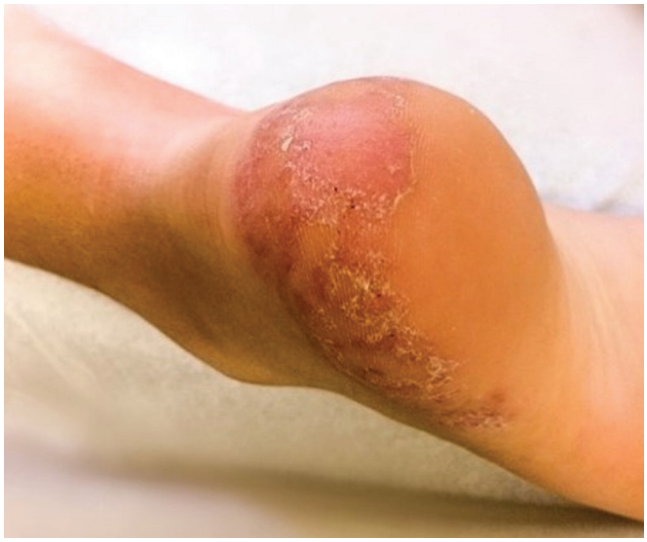

Figure 2. *Chronic cutaneous lupus erythematous: Erythematous to violaceous, hyperkeratotic papules and plaques on the heels.*

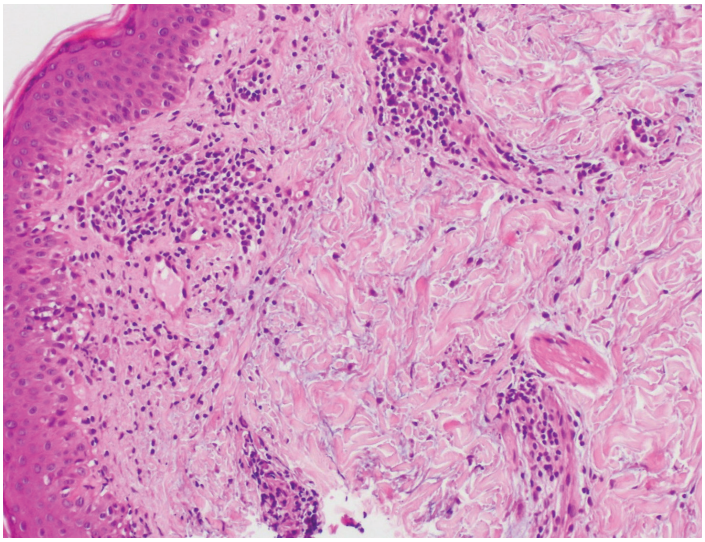

Figure 3. *Histopathological examination: ortokeratotic hyperkeratosis, and multifocal areas of interface dermatitis with slight perivascular infiltrates of mononuclear cells in the papillary and reticular dermis, H&E (200x).*

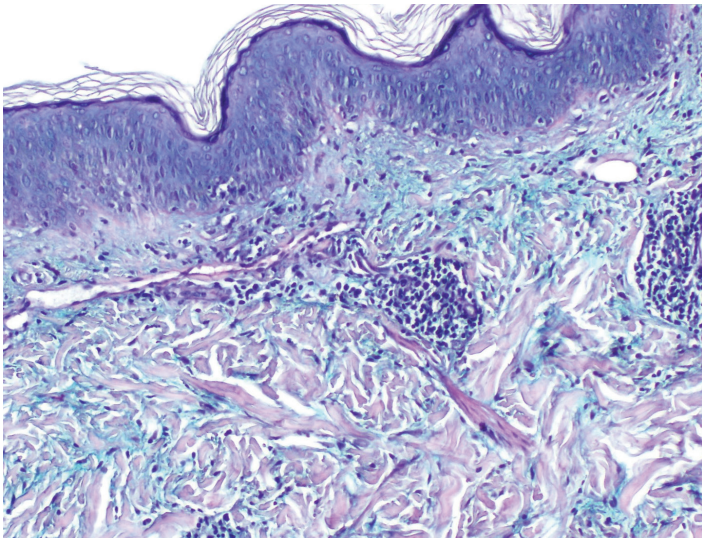

Figure 4. *Histopathological examination: deposition of mucin between collagen fibers in the dermis, alcian blue stain (400x).*

were no other significant symptoms or signs.

The analytical study demonstrated elevated sedimentation rate (24mm), antinuclear (1/640), anti-centromere (23 U/ml), and anti-Saccharomyces cerevisiae (IgA 42.5 U/ml; IgG 81.2 U/ml) antibodies. Capillaroscopy was suggestive of Raynaud phenomenon. Pulmonary function tests, chest radiography, and computed tomography showed no significant alterations.

A skin biopsy was performed on the left arm. Histopathological, immunohistochemical, and direct immunofluorescence examination were suggestive of lupus erythematosus (**Figure 3**).

Accordingly, we assumed the diagnosis of cutaneous lupus erythematous (CLE) with chronic and acute presentations. The patient started oral hydroxychloroquine 6mg/kg/day with resolution of all the lesions after 1 month of treatment. Of note, his sister, a CGD-carrier, was recently diagnosed with CLE, suggesting a shared genetic susceptibility.

Case Discussion

CGD is an autosomal recessive or X-linked primary immunodeficiency disorder, characterized by defective functioning of nicotinamide adenine dinucleotide phosphate (NADPH) enzyme responsible for generating reactive oxygen species after pathogen phagocytosis [1]. Recurrent or persistent infections are commonly observed in patients with CGD. Impaired phagocytosis results in delayed clearance of certain bacteria, fungi, and damaged cells [2]. It has been hypothesized that repeated antigen stimulation by non-phagocytosed bodies can, theoretically, lead to chronic inflammation and promote the overproduction of autoantibodies. This could predispose the patient to a broad variety of autoimmune diseases, like inflammatory bowel disease or lupus erythematous [3-8]. Consequently, in genetically predisposed individuals, chronic exposure to pathogens may represent the primary trigger for the development of autoimmunity. It was recently shown that activated CD4+ lymphocytes in murine CGD models have a strong tendency towards the Th1 pattern of cytokine production, leading to excessive inflammation and dominant production of IL-17 [2]. Iatrogenic factors, which could impact autoimmunity in CGD patients include trimethoprim-sulfamethoxazole, itraconazole, voriconazole, or IFN-γ, but current data lack the statistical power to address the potential contribution of any particular drug on the development of autoimmune diseases [3,6]. Despite the immunocompromised state of CGD, prednisone and other immunosuppressive drugs are often needed in systemic lupus erythematosus. For the cutaneous presentation, hydroxychloroquine is a good option for treatment [9]. Owing to the significant association of pediatric CLE with systemic lupus erythematous, close follow-up is recommended [10]. The presented clinical case highlights the fact that, although infrequent, autoimmune diseases should

be considered in the differential diagnosis of new cutaneous lesions in CGD patients.

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