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LETTER TO EDITOR

Unusual Severe Seborrheic Dermatitis in Two Siblings with Autosomal Recessive Chronic Granulomatous Disease

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To the Editor

Dermatitis generally presents in the eczematous form in eyelids, periorbital skin, nares, perioral skin, and ears. There are several types of dermatitis classified based on clinical presentation and characteristics. Seborrheic dermatitis (SD) or seborrhea is an inflammatory skin disease whose pathophysiology is not completely understood. In infants, SD usually presents as yellow scales on the scalp, while in adolescents and adults, it typically presents as flaky, greasy, erythematous patches on the scalp, nasolabial folds, anterior chest, or upper back. The identification of SD is based on the location and appearance of the lesions, and the skin biopsy usually reveals the presence of epidermal parakeratosis and spongiosis [1]. Primary immunodeficiencies (PID) are inborn errors of immunity that lead to susceptibility to infections. Skin manifestations are present in approximately 40% of pediatric cases of PID [2]. Chronic granulomatous disease (CGD) is a PID caused by mutations in any of the components of the NADPH oxidase system complex (gp91, p22, p47, p67, and p40phox) resulting from mildly reduced to absent oxidative burst of phagocytes. Patients with CGD are susceptible to infections as a consequence of the defective microbicidal activity of phagocytes. Although dermatological manifestations in patients with CGD are associated mainly with systemic or deep infections, SD is rare in these patients and, to date, only one case of SD affecting a CGD patient has been documented [3]. Here we report two female siblings ages 17 and 24 years old, born from consanguineous parents and affected with autosomal recessive (AR) CGD and clinical findings compatible with SD (Fig. 1a). Patient 1 was born in 1992 and presented her first symptoms at the age of 8 months when she developed recurrent furunculosis affecting the cervical, inguinal, and epigastric regions. At the age of 11 years, she developed dry eczema predominantly in the face and diffused desquamation on the back of the neck and scalp. The lesions consisted of plaques with well-defined borders and yellowish adherent scales without pruritus. After the diagnosis of SD, the patient developed pyoderma. At the age of 13 years, she developed conjunctivitis and cervical and inguinal lymphadenitis with high fever. Histologic examination of the lymph node revealed chronic inflammation and granulomas and *Staphylococcus aureus* was isolated. For the remaining 12 years, the patient suffered bronchospasm and infectious episodes such as recurrent pneumonia, bacterial conjunctivitis, skin infections, and cervical abscesses. Finally, in her last hospitalization, she developed acute abdominal pain due to a liver abscess. Patient 1 was treated with oxacillin and metronidazole for 32 days, amikacin for 15 days, and later replaced by vancomycin/clindamycin and ceftazidime for 45 days for those acute occurrences. Patient 2 was born in 1999 and is the younger sister of Patient 1. She presented her first symptoms at the age of 5 months when she developed cervical lymphadenitis with granulomas. For the next 10 years, the patient remained asymptomatic until she developed recurrent furunculosis in several parts of the body as well as pneumonia, otitis, and cystitis. Then, at the age of 13 years, she developed seborrheic dermatitis as her older sister. The patient suffered SD lesions in distinct areas, such as the external ear, retroauricular region, back of the neck, and scalp which progressed from light yellow to erythematous scales. The desquamations with crusts entirely affixed to the scalp resulted in significant alopecia in the patient (Fig. 1b). Both patients were treated with full dose of sulfamethoxazole-trimethoprim and itraconazole for

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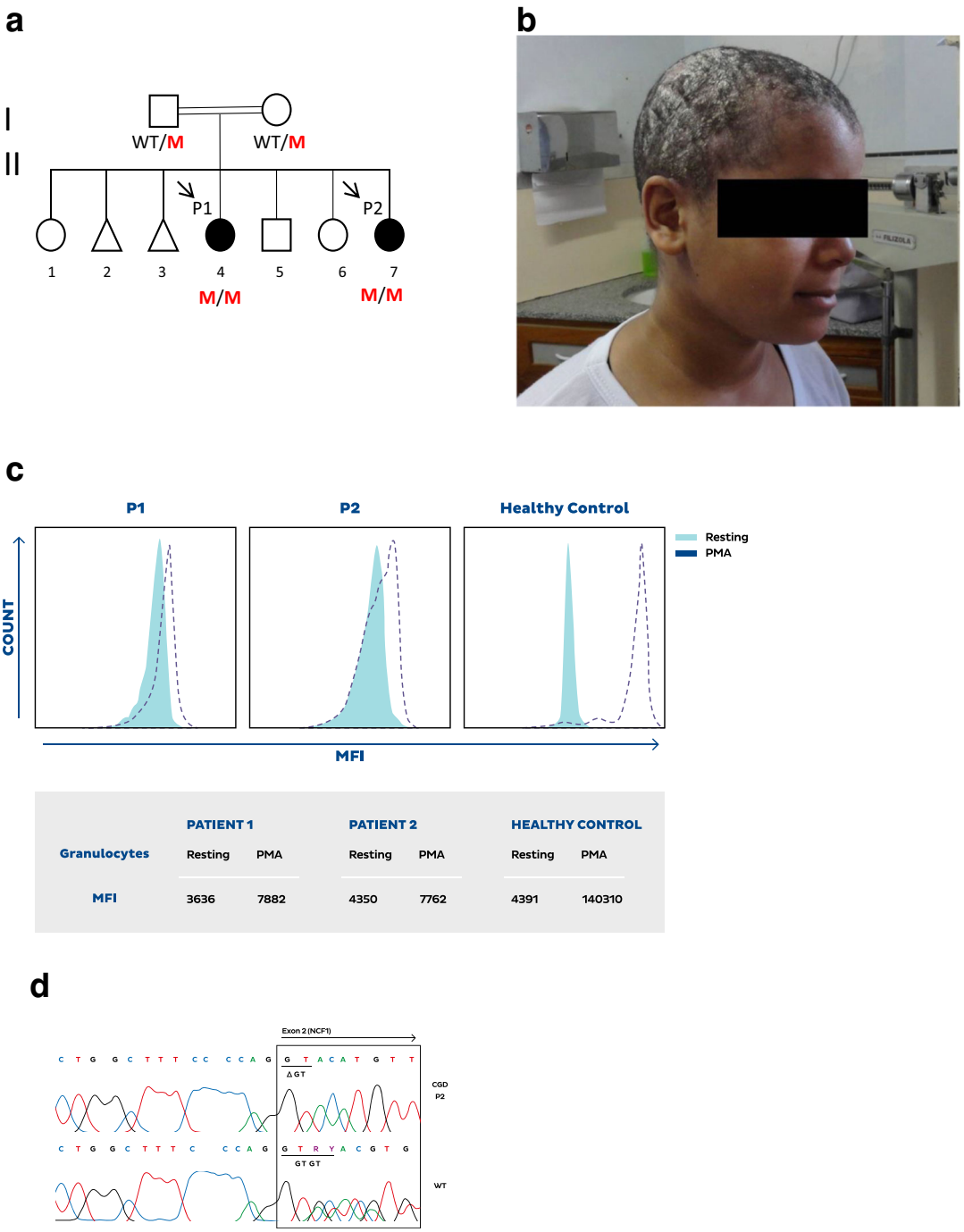

Fig. 1 Clinical manifestations, biochemical, and genetic analyses of sibling patients. **a** Family pedigree; females (circle), male (square), miscarriage (triangle), and CGD siblings with the *NCF1* genotype (black circles and arrows). M, NCF1 mutation; WT, wild type. **b** Severe seborrheic dermatitis on scalp at 13 years old in patient 2. **c** DHR assay by flow cytometry of the patients and a healthy control before (resting, gray line) and upon stimulation for 30 min with PMA (30 nM, black line). Results expressed as mean fluorescence intensity (MFI) in granulocytes producing H_2O_2. **d** Exon 2 Sanger sequencing of patient 2 (representative mutation found in both patients) and a healthy control (WT)

45 days regarding the SD. Daily prophylaxis with sulfamethoxazole-trimethoprim and itraconazole was recommended after acute treatments for both patients. Patient skin biopsies were not performed. The clinical manifestations and the family history directed the investigation towards the diagnosis of AR-CGD. The hypothesis of impaired oxidative burst of phagocytes was tested by flow cytometry using the dihydrorhodamine-123 (DHR) assay in both sisters, revealing decreased production of reactive oxygen species (ROS) by granulocytes with respect to a healthy control (Fig. 1c). Sequencing of the neutrophil cytosolic factor 1 gene (*NCF1*) in genomic DNA from both patients revealed a GT deletion

(ΔGT) at the beginning of exon 2, predicted to cause a frameshift and a premature stop codon (p.Tyr26fs*26) (patient 2, Fig. 1d); in addition, both parents were heterozygous for the mutation. Mutations in *CYBB* (gp91phox) are responsible for X-linked CGD (XL-CGD) in approximately 65–70% of the CGD cases in the western world. The remaining 35% of cases are due to mutations in other components of the NADPH system and cause AR-CGD. The mutation identified in both patients affects *NCF1* that encodes for the p47phox subunit of the NADPH oxidase complex. This mutation (ΔGT) affects approximately 95% cases of patients with p47phox deficiency and results by recombination events between wild-type *NCF1* and two pseudo-*NCF1* genes (Ψ*NCF1*) that contain the GT deletion [4].

In XL-CGD patients, ROS production is usually undetectable, and the clinical manifestations occur early in life. On the other hand, patients with AR-CGD generally present residual respiratory burst activity, which is responsible for the delay of symptoms and the diagnosis later in life. In the cases described here, patient 1 showed several symptoms during childhood but was diagnosed only at 11 years old, while patient 2 remained asymptomatic for 10 years before she was diagnosed at age of 13 years. In a cohort of Latin American CGD patients ($N = 71$), recurrent pneumonia, lymphadenopathy, and granulomata were the most frequent clinical manifestations (76.8%, 59.4%, and 49.3%, respectively). However, in AR-CGD patients due to *NCF1* mutations ($N = 16$), skin manifestations were the second (58%) most frequent clinical presentation [5]. In patient 1, the first manifestation was furunculosis at the age of 8 months, and she developed SD 10 years later. Dermatological manifestations in CGD, when present, include mainly dermatitis associated with infectious complications with diverse etiology. The precise pathogenesis of SD is still a matter of controversy. *Malassezia* spp. in the skin microbiome of the scalp have been considered the causative agent of SD. Importantly, when lesions localize in regions as the scalp, differential diagnosis is necessary and a skin biopsy showing severe lymphocytic and prominent spongiosis may be a favorable criterion for the diagnosis of SD. However, immunohistochemistry including Ki-67, keratin 10, caspase-5, and GLUT-1 might not be sufficient to differentiate psoriasis from SD [7]. The treatment for SD includes keratolytic agents, corticosteroids, and antifungal agents. Low-dose oral isotretinoin can be of benefit in the eradication of yeast colonization in the scalp in patients with moderate to severe SD [6]. The incidence of SD has been reported from early to late onset, in both children and adults, as it was the case with our two siblings (11 and 13 years old). On the other hand, SD is a rare skin condition in patients with CGD and has only been described once in a Mexican patient [3]. Our results suggest that severe and recurrent SD could be an unusual clinical manifestation in patients with CGD due to mutations in *NCF1*. This report highlights the relevance of the differential diagnosis of PID patients with severe skin manifestations, contributing to the appropriate management of the disease.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Committee This study was approved by the Ethics and Research Committee for Humans at the Institute of Biomedical Sciences, University of São Paulo, in accordance with the Declaration of Helsinki. Patients or parents provided written informed consent.

References

1. Clark GW, Pope SM, Jaboori KA. Diagnosis and treatment of seborrheic dermatitis. Am Fam Physician. 2015;91:185–90.
2. Berron-Ruiz L, Morin-Contreras A, Cano-Garcia V, Yamazaki-Nakashimada MA, Gomez-Tello H, et al. Detection of inheritance pattern in thirty-three Mexican males with chronic granulomatous disease through 123 dihydrorhodamine assay. Allergol Immunopathol (Madr). 2014;42:580–5.
3. Luis-Montoya P, Saez-de Ocariz Mdel M, Vega-Memije ME. Chronic granulomatous disease: two members of a single family with different dermatologic manifestations. Skinmed. 2005;4:320–2.
4. Vazquez N, Lehrnbecher T, Chen R, Christensen BL, Gallin JI, et al. Mutational analysis of patients with p47-phox-deficient chronic granulomatous disease: the significance of recombination events between the p47-phox gene (NCF1) and its highly homologous pseudogenes. Exp Hematol. 2001;29:234–43.
5. de Oliveira-Junior EB, Zurro NB, Prando C, Cabral-Marques O, Pereira PV, Schimke LF, Klaver S, Buzolin M, Blancas-Galicia L, Santos-Argumedo L, Pietropaolo-Cienfuegos DR, Espinosa-Rosales F, King A, Sorensen R, Porras O, Roxo-Junior P, Forte WC, Orellana JC, Lozano A, GalicchioM, Regairaz L, Grumach AS, Costa-Carvalho BT, Bustamante J, Bezrodnik L, Oleastro M, Danielian S, Condino-Neto. Clinical and genotypic spectrum of chronic granulomatous disease in 71 Latin American patients: first report from the LASID registry. A Pediatr Blood Cancer. 2015;62:2101–7.
6. Kamamoto CSL, Nishikaku AS, Gompertz OF, Melo AS, Hassun KM, et al. Cutaneous fungal microbiome: Malassezia yeasts in seborrheic dermatitis scalp in a randomized, comparative and therapeutic trial. Dermatoendocrinol. 2017;9:e1361573.
7. Park JH, Park YJ, Kim SK, Kwon JE, Kang HY, Lee ES, et al. Histopathological differential diagnosis of psoriasis and seborrheic dermatitis of the scalp. Ann Dermatol. 2016;28:427–32.