Refractory pruritus responds to dupilumab in a patient with TTC7A mutation

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INTRODUCTION

Tetratricopeptide repeat domain 7A (TTC7A) mutations are known to cause multiple intestinal atresia (MIA), early onset inflammatory bowel disease, and combined immunodeficiency. Skin involvement appears mainly after the age of 2 years. This case is the first report of eczematous lesions and refractory chronic pruritus in a TTC7A-deficient patient. Dupilumab was successfully used to treat these manifestations.

CASE PRESENTATION

A 5-year-old girl, born to non-consanguineous parents, presented with MIA. She had gastric outlet obstruction and ileal atresia requiring a gastrojejunal anastomosis and an ileocaecal resection early on. Total parenteral nutrition was required. Intestinal biopsies revealed severe colitis with apoptosis and dense eosinophilic infiltration. At 3 months of age, monocytosis, hypogammaglobulinemia, and lymphopenia 0.8 × 10^9/L with decreased T helper lymphocytes (CD4+), particularly in naïve CD4 lymphocytes (CD31+/CD4+/CD45RA) and in B lymphocytes (CD19+) (Table I), led to the diagnosis of profound combined immunodeficiency. She experienced multiple central line infections and 1 episode of *Pneumocystis jiroveci* pneumonia.

Genetic testing showed 3 heterozygote mutations on the *TTC7A* gene: i) c.518G>A (p.Gly173Asp) mutation of paternal inheritance, never reported before and of unknown significance; ii) c.1000_1001+2delAAGT mutation of maternal inheritance, described in patients with MIA and immunodeficiency[1,2]; and iii) c.2170C>A (p.Gln724Lys) of paternal inheritance which is a rare variant with unknown significance. These genetic findings together with the clinical and biologic manifestations confirmed the diagnosis of TTC7A deficiency.

Abbreviations used:

IL:	interleukin
MIA:	multiple intestinal atresia
TTC7A:	tetratricopeptide repeat domain 7A

By the age of 3 years, she developed pruritus. Clinical examination showed diffuse xerosis, and excoriated and eczematous lesions (Fig 1, *A*). Skin biopsy showed hyperorthokeratosis consistent with ichthyosis (Fig 2) previously described in TTC7A mutation.[3] It also revealed spongiosis, primarily within the follicular epithelium, associated with a prominent eosinophilic infiltrate. The complete blood count showed hypereosinophilia (1.7 10^9/L [normal range, 0-0.4 10^9/L]). The serum IgE level was high (1766 kU/L [normal range, 0-214 kU/L]). Renal function and bilirubin levels were within normal limits (Table I). She was closely followed up for nutritional deficiencies, and iron deficiency was corrected without improvement of her skin condition.

Emollients and topical corticosteroids (betamethasone valerate ointment 0.1% and betamethasone dipropionate ointment 0.05%) twice per day led to initial improvement of the eczematous lesions.

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Table I. Immunologic parameters at 3 months and 3 years of age with local age-specific reference values

	Patient values*			
Parameter	**3 months old**	**Reference values**	**3 years old**	**Reference values**
Total lymphocytes, × 10^6/L	2200	4400-9000	400	2800-7300
CD3+, × 10^6/L (%)	990 (45)	2438-5775 (53-86)	128 (32)	1872-4307 (52-83)
CD4+, × 10^6/L (%)	660 (30)	1794-4425 (34-66)	88 (22)	1140-2773 (29-59)
CD8+ high, × 10^6/L (%)	770 (35)	528-1505 (9-26)	32 (8)	454-1470 (10-30)
CD31+CD45RA/CD4+, × 10^6/L (%)	184 (28)	(59-84)	30 (35)	(44-76)
CD19, × 10^9/L (%)	374 (17)	470-2790 (8-31)	220 (55)	330-2227 (8-37)
CD56+CD3-, × 10^6/L (%)	622 (28)	112-831 (2-13)	60 (15)	81-823 (2-17)
IgG, g/L	1.31	1.10-7.00		
IgA, g/L	0.20	0-0.30		
IgM, g/L	<0.05	0.20-0.90		
IgE, kU/L			1766	0-214
Eosinophils, × 10^6/L	600	0-400	1700	0-400

g/l, Gram/liter; *kU/l*, kilounit/liter.
*The numbers in parentheses indicate the proportion of the lymphocyte subtype relative to the total lymphocyte count.

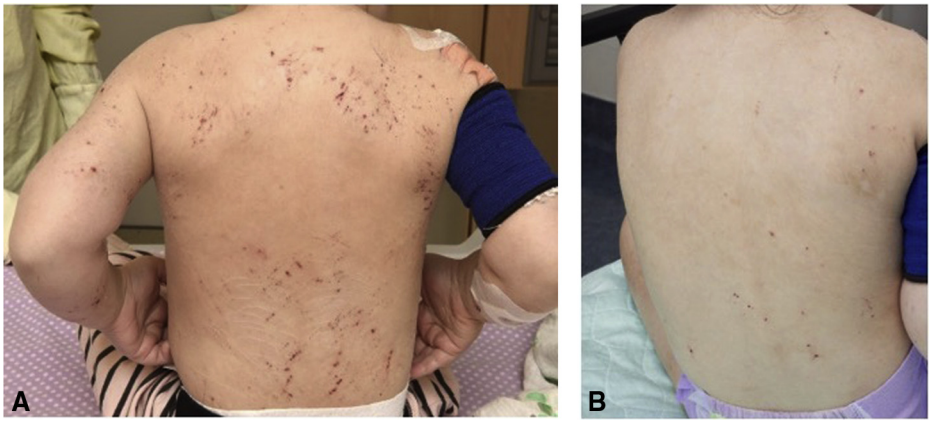

Fig 1. **A**, Clinical presentation of the back at 3 years of age with diffuse xerosis, excoriated and eczematous lesions. **B**, Post-inflammatory hyperpigmentation with scarce excoriated lesions of the back after 3 months of dupilumab.

However, pruritus increased over time. Multiple antihistamine treatments (diphenhydramine 5 mg/kg/day, desloratadine 2.5 mg/day (50% of the adult dose), hydroxyzine 2 mg/kg/day) were ineffective. In addition, gabapentin (up to 35 mg/kg/day), clonidine (0.005 mg/kg/day), mirtazapine 7.5 mg/day (50% of the adult dose), and amitriptyline (0.5 mg/kg/day) were unsuccessful in relieving pruritus. The use of oral corticosteroids (1 mg/kg/day) provided only partial relief. Given the patient's hypereosinophilia, mepolizumab (anti-IL5 agent) was administered subcutaneously at a dose of 50 mg every month for 12 months without improvement.

At the age of 4, her quality of life was profoundly altered; her constant impulsive scratching caused self-mutilation, insomnia, and sudden aggressive outbursts of anger, hostility, and crying. She suffered from multiples episodes of sepsis secondary to skin excoriation.

At 5 years of age, she was hospitalized for *Staphylococcus aureus* bacteremia secondary to central line infection. An intravenous 14-day course of vancomycin 70 mg/kg/day was introduced. After 9 days of antibiotic treatment, her pruritus worsened, and she developed a widespread vesiculobullous eruption. Skin biopsy revealed a subepidermal blister with neutrophils aligned along the dermoepidermal junction. Direct immunofluorescence showed linear IgA deposits on the basal membrane confirming the diagnosis of linear IgA bullous dermatosis—probably due to vancomycin. Methylprednisolone 1 mg/kg/day (20 mg/day) was introduced intravenously with the complete resolution of skin lesions without recurrence. For the first time, the patient experienced complete relief of her pruritus. As

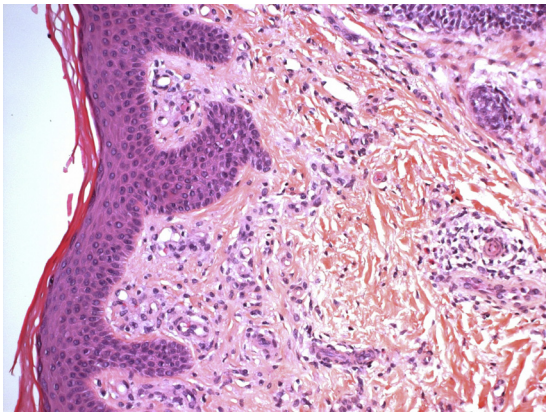

Fig 2. Skin biopsy of the right arm at the age of 3 years demonstrates the presence of hyperorthokeratosis with a thinned granular layer consistent with ichthyosis. (Hematoxylin-eosin stain; original magnification: ×200.)

methylprednisolone was progressively tapered, pruritus relapsed whenever doses were below 0.5 mg/kg/day (10 mg/day), preventing the cessation of treatment.

Off-label treatment with dupilumab (anti-interleukin [IL]-4, -13) 100 mg subcutaneously every 2 weeks was requested for compassionate use in spite of her young age. A few days after the first dupilumab injection, a significant improvement of pruritus was observed. During the 6 following months, the methylprednisolone was tapered to a physiologic dosage without relapse of pruritus or eczematous lesions (Fig 1, *B*). Her quality of life improved significantly. At 1-year follow-up, there was no relapse or pruritus or eczematous lesions.

DISCUSSION

TTC7A deficiency is an autosomal-recessive disorder known to cause MIA, early onset inflammatory bowel disease, and severe combined immunodeficiency.[4,5] Reportedly, skin manifestations are absent at birth and appear after the age of 2 years.[3,6] A study of 13 patients from a consanguineous TTC7A-deficient family with a 211G>A homozygous missense mutation responsible for enteropathy, lymphopenia, and alopecia syndrome, showed 5 members with patchy alopecia; 1 with psoriasis, and 4 with onychodystrophy described as subungual hyperkeratosis.[3,7] Two unrelated patients with MIA-CDI also reported skin involvement.[6] The first patient presented a progressive xerosis, epidermal thickening of the extremities, and palmoplantar keratoderma at the age of 6 years, and the second one presented xerosis at the age of 3 years. Our case is the first to report eczematous lesions and recalcitrant chronic pruritus in TTC7A deficiency.

The physiopathology of this condition is multifold. Studies suggest that the TTC7A mutation leads to an inappropriate activation of the Rho kinase-signaling pathway, which plays an important role in cell adhesion, polarization, differentiation, and apoptosis in gastrointestinal epithelia, keratinocytes, and lymphocytes.[4,5] A study in murine models showed that TTC7A-mutated fibroblasts are potent triggers of epithelial proliferation.[4] The comparison of TTC7A-mutated mice (flaky-skin mice) and humans show similar skin changes, both clinical and histopathologic, consistent with abnormal epidermal maturation and hyperproliferation.[4,7] These epidermal changes probably lead to barrier dysfunction, similarly to atopic dermatitis.

In this case, biopsy revealed spongiosis and a rich eosinophilic infiltrate suggestive of a Th2 immune response. Dupilumab is a monoclonal antibody against the alfa subunit of the IL-4 receptor, preventing interaction of cytokines IL-4 and IL-13 with their receptors. It is approved by the Food and Drug Administration for moderate-to-severe atopic dermatitis in patients older than 6 years of age. The literature reports successful treatment of chronic pruritus with dupilumab.[8] Oetjen et al[9] showed that type-2 cytokines activate itch-sensory neurons, thereby their blockade can improve the pruritus. In the same way, dupilumab demonstrated significant improvement of the recalcitrant pruritus in our patient. This case provides new insight into dermatologic manifestations of TTC7A mutations and demonstrates a novel therapeutic strategy to manage them.

Conflicts of interest

Dr Danielle Marcoux has been primary investigator, speaker, and on advisory board for Sanofi Genzyme. Drs Yassaman Alipour Tehrany, Louis Marois, Caroline Colmant, Valérie Marchand, Victor Kokta, Jérôme Coulombe, Elie Haddad, and Catherine McCuaig have no conflicts of interest to declare.

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