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Case study

Loss of ADAM17 is associated with severe multiorgan dysfunction ☆

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Summary ADAM metallopeptidase domain 17 (ADAM17) is responsible for processing large numbers of proteins. Recently, 1 family involving 2 patients with a homozygous mutation in *ADAM17* were described, presenting with skin lesions and diarrhea. In this report, we describe a second family confirming the existence of this syndrome. The proband presented with severe diarrhea, skin rash, and recurrent sepsis, eventually leading to her death at the age of 10 months. We performed exome sequencing and detailed pathological and immunological investigations. We identified a novel homozygous frameshift mutation in *ADAM17*

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(NM_003183.4:c.308dupA) leading to a premature stop codon. $CD4^+$ and $CD8^+$ T-cell stimulation assays showed severely diminished tumor necrosis factor–α and interleukin-2 production. Skin biopsies indicated a focal neutrophilic infiltrate and spongiotic dermatitis. Interestingly, the patient developed unexplained systolic hypertension and nonspecific hepatitis with apoptosis. This report provides evidence for an important role of *ADAM17* in human immunological response and underscores its multiorgan involvement.

1. Introduction

ADAM metallopeptidase domain 17 (ADAM17) is a sheddase belonging to the ADAM family of disintegrins and metalloproteases. Because of its wide variety of ligands such as epidermal growth factor receptor ligands, tumor necrosis factor (TNF)–α, and angiotensin I converting enzyme 2, ADAM17 is crucially involved in various pathological conditions including cancer, inflammation, neurodegeneration, and fibrosis. More than 70 different substrates for ADAM17 have been reported [1]. Recently, 2 siblings were described with a homozygous loss of function mutation in the gene encoding for *ADAM17* [2]. Whereas 1 sibling died at the age of 12 years, the other sibling presented in adulthood and experienced repeated skin infections only. Mechanistic data and assessment of different organ systems potentially affected by a loss of ADAM17 function were limited in this report. Here we report a second family with a novel mutation in the *ADAM17* gene confirming the existence of this new rare syndrome and provide evidence for a multiorgan involvement.

2. Clinical history

2.1. General history and infectious manifestions

The examined family consisted of 5 family members with the proband being the third child, a girl, of healthy Armenian parents. There was no history of consanguinity. The pregnancy was uneventful except for intrauterine diagnosed oligohydramnios and growth restriction. After a full-term vaginal delivery, birth weight was 2790 g (20th-50th percentile). At birth, the main clinical feature of the infant was its skin that was covered by a collodion membrane, which coincided with diffuse erythema. Except for an ear tag, no other dysmorphic features were present. Apart from the affected child, the siblings and parents were examined clinically by a staff geneticist for dysmorphic features, which were not found. She was discharged soon after birth but readmitted 13 days after birth because of persistent skin rash, diarrhea, and weight loss. From the first hospital admission until her death, there were numerous (>12) episodes with fever and irritability and, for some episodes, clinical signs of sepsis with tachycardia and cold peripheries. Febrile episodes were accompanied by significant elevations of blood inflammatory markers, for which antibiotic therapy was empirically started. C-reactive protein was intermittently elevated with a peak level of 72 mg/mL; in-between levels were normal (<5 mg/mL). Leukocytes were elevated most of the time, with levels around 15×10^9/L and a peak level of 34×10^9/L. Blood cultures taken during these incidents were only positive on 3 of these episodes. Enterogenic bacteria, *Acinetobacter* spp (2×), and *Escherichia coli* (1×) were cultured. After initiation of selective intestinal decontamination, that is, reducing the concentration of potentially pathogenic bacteria and fungi using tobramycin, colistin, and amphotericin B, there were no more septic/bacteremic events. After prolonged hospitalization in different hospitals, the patient ultimately developed respiratory insufficiency related to a respiratory syncytial virus and died at the age of 10 months because of refractory hypoxia. Autopsy was not granted by the family.

2.2. Cutaneous involvement

Tender skin lesions were seen within 7 days after birth. The skin felt dry, rough, and scaly, reminiscent of atopic dermatitis/ichthyosis vulgaris (Fig. 1). There were diffuse generalized pustular rash and erythema with yellow crusted scales, similar to those seen in seborrheic dermatitis, over the scalp and face (periocular, cheek, chin, jaw, upper lip) and in the folds of axillae and groins. The clinical picture was suggestive of acrodermatitis enterohepathica but failed to respond to zinc supplementation. Multiple bacterial swabs of the skin grew *Staphylococcus aureus*. Hair on scalp and eyebrows was present at birth but shed soon thereafter. Hair growth returned at the age of 6 months. The nails were not affected. The severity of skin abnormalities was episodic in nature and appeared to coincide with the severity of intestinal symptoms. Dermatological treatments included corticosteroids, antimycotics/antibiotics, and plain ointments, with some clinical response. The skin infections responded best to systemic broad-spectrum antibiotics.

2.3. Gastrointestinal and hepatic manifestations and growth

Severe watery diarrhea developed in the first week of life. Diarrhea did not completely disappear after discontinuation of feeding, suggesting a combination of osmotic and secretory diarrhea. Feeding in the form of an elemental amino acid–based formula was restarted but did not prevent novel episodes of loose to watery stools. Mucus was also