Protein-losing enteropathy and joint contractures caused by a novel homozygous ANTXR2 mutation

Edith Schussler¹
Rita V Linkner²
Jacob Levitt²
Lakshmi Mehta³
John A Martignetti¹,³
Kimihiko Oishi¹,³

¹Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ²Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ³Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract: Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disorder and an allelic form of hyaline fibromatosis syndrome that is caused by mutations in the ANTXR2 gene encoding the transmembrane anthrax toxin receptor 2. Its main features include characteristic skin lesions, joint contractures, persistent diarrhea, and failure to thrive due to accumulation of hyaline material in multiple organs. The resulting severe malnutrition can cause death in early infancy. Because of its rarity and high fatality rate, timely diagnosis is difficult and ISH may be underdiagnosed. In this report, we describe a 10-month-old male with severe protein-losing enteropathy, skin lesions, and painful joint contractures, diagnosed with ISH based on skin histopathology and identification of a novel homozygous ANTXR2 mutation, c.1127_1128delTG (p.V376Gfs*14). While its clinical outcome is poor without curative treatment, establishing a diagnosis of ISH starting from clinical suspicion to molecular analysis is important for appropriate medical management and for risk and carrier assessment of family members.

Keywords: infantile systemic hyalinosis, hyaline fibromatosis syndrome, juvenile hyaline fibromatosis, ANTXR2, enteropathy

Introduction

Infantile systemic hyalinosis (ISH) (MIM #228600) is a rare autosomal recessive disorder characterized by painful joint contractures, skin hyperpigmentation over bony prominences, thickening of the skin with pearly papules, osteoporosis, bone fractures, persistent diarrhea, and failure to thrive.¹,² ISH is an allelic form of hyaline fibromatosis syndrome³ caused by mutations in the ANTXR2 (also known as CMG2) gene (MIM #608041), which encodes the transmembrane anthrax toxin receptor 2/capillary morphogenesis protein-2.⁴ ISH generally results in life-threatening malnutrition that leads to early death in infancy, unlike its milder allelic condition, juvenile hyaline fibromatosis (JHF).²,⁵,⁶ While the genetic basis is now known, the molecular pathogenesis of hyaline fibromatosus syndrome is unclear. It is hypothesized that disruption of this membrane protein causes accumulation of hyaline materials and tissue damage/malfunction in multiple organs.⁷ Owing to its rarity and associated rapid clinical deterioration, timely diagnosis of ISH is difficult and, as a result, it may be underdiagnosed. Here, we report a case of ISH in an infant who was referred to us for clinical care and highlight the presentation and steps leading to identification of a novel diagnostic homozygous mutation, c.1127_1128delTG (p.V376Gfs*14), in ANTXR2.
Case report

The patient was an Asian 10-month-old male (individual II-3 in Figure 1) who was born full term with a birth weight of 3.75 kg (66 percentile). His parents were half-first cousins and had 2 healthy daughters (Figure 1). The proband had mild contractures in major joints at birth but was otherwise noted to be healthy. At 5 months of age, his joint contractures had progressively worsened and were associated with pain in his wrists, elbows, shoulders, hips, knees, and ankles. Concurrently, he developed dark brown/black spots on his knuckles, ankles, back, and neck. Initially, arthrogryposis was suspected, and so he received physical therapy, which resulted in a femur fracture. At that time, he also developed persistent protein-losing enteropathy with significant weight loss. He came to the USA for additional medical care at the age of 10 months. According to the family, there were no other family members who had similar symptoms as the patient.

On presentation, the most striking features were the severe malnutrition (5 kg; <3 percentile) and constant irritability. On physical examination, significant joint contractures of the wrists, knees, hips, and ankles were noted (Figure 2A and B). Oral mucosa demonstrated gingival hyperplasia (Figure 2C). There were generalized sclerodermatous changes of the skin, most prominently in the left lower extremity (Figure 2B). Skin was significant for pearly, erythematous papules and indurated plaques located symmetrically on the back (Figure 2C and D). Similar indurated plaques that were more erythematous than violaceous were also seen on the posterior scalp (Figure 2E). The perianal area revealed multiple coalescent skin-colored, indurated papules involving the perineum (Figure 2F). Due to long-standing malnutrition, the child had multiple electrolyte abnormalities including a nonanion gap acidosis, hyponatremia, hyperkalemia, and hypoalbuminemia.

A biopsy was obtained from one of the violaceous, indurated plaques on the infant’s back, and histopathologic analysis revealed an amorphous eosinophilic, hyaline material with spindle cells deposited in the superficial and deep dermis consistent with ISH (Figure 3A and B). Some of the cells in the hyaline material appeared to lie in lacunae, giving it a chondroid-like appearance (Figure 3B). The deposits were Periodic acid–Schiff staining positive (Figure 3C), diastase resistant, and did not stain with Alcian blue. No elastic fibers were identified on a Verhoeff’s Van Gieson stain (Figure 3D). These findings were consistent with ISH.

To confirm the diagnosis, we sequenced all 17 coding exons and intron/exon boundaries, of the ANTRX2 gene using genomic DNA isolated from the patient and his mother. A homozygous 2-bp TG deletion in exon 14, which predicted a frameshift mutation, c.1127_1128delTG (p.V376Gfs*14), was identified in the patient. Consistent with her presumed...
carrier status, the mother was heterozygous for the ANTXR2 mutation (Figures 1 and 4). The father’s sample was not available for analysis. Written informed consent for publication of the patient’s clinical information, including photographs, was obtained from the patient’s parents.

**Discussion**

The approach to diagnosing rare disorders can be particularly difficult. Identifying certain characteristic features can help navigate toward the selection of the appropriate targeted molecular tests. For our case, the combination of skin lesions,
families have been identified. Nearly all of the reported 37 different ISH/JHF-causing mutations in 67 patients and 49 heterozygosity within one of the hotspot mutations and the importance of the C-terminal structure of the protein. Intriguingly, while the role of the ANTRX2 protein as an anthrax toxin receptor is known, the molecular derangements resulting in the unique symptoms of ISH/JHF, and possible phenotype/genotype correlation, are poorly understood. The protein’s von Willebrand A domain, which binds to both lamin and collagen IV, suggests its role in basement membrane matrix assembly and endothelial cell morphogenesis, resulting in tissue damage and/or multiple organ malfunction. Despite severe musculoskeletal involvement, cognitive function is most likely spared because of the lack of ANTRX2 protein expression in the brain. In general, precise molecular diagnosis is imperative not only for medical management of the patient but also for risk and carrier assessment of family members. Our patient’s condition at the time of presentation to our institution and diagnosis was refractory to nutritional support and electrolyte correction, and he died at 11 months of age. It is unknown if earlier attempts at parenteral nutrition would have changed this outcome. A recent study suggested that proteasome inhibitors might represent therapeutic candidates depending on the severity of the ANTRX2 mutation. Ultimately, if clinical suspicion leads to earlier molecular diagnosis of ISH, this would allow for more meaningful assessment of candidate therapeutics in treatment and support of this disease.

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Disclosure

The authors report no conflicts of interest in this work.

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