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CASE REPORT

Infantile systemic hyalinosis: report of a case from Bahrain and review of literature

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ABSTRACT

Background: Infantile systemic hyalinosis (ISH), an allelic form of hyaline fibromatosis syndrome, is a rare fatal autosomal recessive disorder that is caused by mutations in the *CMG2/ANTRX2* gene encoding the transmembrane anthrax toxin receptor 2. It has a compound of features due to the accumulation of hyaline material in multiple organs including characteristic skin lesions, joint contractures, persistent diarrhea, and failure to thrive. The resulting severe malnutrition can be the cause of death in early infancy. Due to its rarity and early high fatality rate, timely diagnosis is difficult, and children with ISH may die undiagnosed.

Case Presentation: In this report, we describe a 3-year-old female diagnosed with ISH after reviewing her clinical and laboratory workup in Salmaniya Medical Hospital. She was diagnosed with ISH based on the clinical presentation of severe skin lesions, painful joint contractures, and later developed renal tubular acidosis. Her diagnosis was confirmed with skin histopathology and identification of homozygous *ANTRX2* mutation, c.652T>C, p.Cys218Arg, and Chr4 (GRCh37): g.80957171A>G.

Conclusion: While the clinical outcome of the disease is poor without curative treatment, establishing an early diagnosis of ISH, beginning with clinical suspicion to molecular analysis, is important for accurate management as well as carrier and risk assessment of family members.

Keywords: Hyaline fibromatosis syndrome, infantile systemic hyalinosis, ISH, juvenile hyaline fibromatosis, ANTXR2.

Introduction

Hyaline fibromatosis syndrome (HFS) (OMIM 228600) is a fatal rare autosomal recessive disorder caused by mutations in the *CMG2* gene (capillary morphogenesis gene 2), also known as *ANTXR2* (anthrax toxin receptor-2), located in chromosome 4q21 (1). It is presumed that alterations in gene *ANTXR2* cause the extravasation of hyaline material through the damaged basement membrane of capillary vessels to the perivascular space, leading to its accumulation in the skin and other organs (2). HFS includes two disorders which are allelic and express the same phenotypic spectrum, infantile systemic hyalinosis (ISH [MIM 236490]), and juvenile hyaline fibromatosis (JHF [MIM 228600]) (1,3). ISH represents the lethal spectrum of the disease, manifesting in the first few weeks of life. JHF, on the other hand, represents the milder form of the disease spectrum, manifesting later in life. The histologic and ultrastructural features of JHF are similar to those of ISH (3).

Infantile systemic hyalinosis affects primarily the skin and mucous membranes, presenting as thickened skin, red hyperpigmented macules/patches over bony prominences of the joints, subcutaneous nodules, pearly papules of the face and neck, and small nodules of the perianal region, ears, or lips. The progressive joint contractures and long bone osteopenia are associated with severe pain with movement and lead to frog-leg position and virtual immobility. Mucosal involvement presents as gingival hypertrophy, curvature of the dental roots, and periodontal ligaments being replaced by hyaline fibrous material (4).

Infantile systemic hyalinosis patients develop protein-losing enteropathy, resulting in chronic diarrhea and ultimately failure to thrive. *ANTXR2* gene is expressed in numerous tissues but not in the brain; therefore, cognitive development is normal. Complications of

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protein-losing enteropathy and failure to thrive can be life threatening (5).

No effective treatment is established for ISH; as a consequence, most patients die at 2 years of age due to recurrent infections and protein-losing enteropathy (1,6).

Diagnosis depends on the clinical histopathology of skin lesions, showing the proliferation of spindle-shaped cells embedded in a homogeneous hyaline-like material in the dermis. Moreover, biochemical alterations in type I and VI collagens in addition to glycosaminoglycans were also reported (1).

Case Presentation

A female baby, with a history of weak intrauterine fetal movements, was born at full term with a birth weight of 3.5 kg to consanguineous healthy parents from Pakistan. She had no feeding problems and was given only formula milk. She was worked up in Pakistan for joint contracture and diagnosed as arthrogryposis multiplex congenita. She first presented to the pediatric department at the age of 1.5 years due to the limitation of movement of both the upper limbs. By reviewing her history, the condition started at the age of 2 months, as the parents noted contracture in the shoulder joint with poor palmar grasp associated with delayed developmental milestones. The patient had a sibling who died of a similar condition at the age of 8 months, as well as three other healthy siblings (Figure 1).

By inspection, the patient had coarse facial features consisting of depressed nasal bridge, saddle nose, wide philtrum, along with gingival hypertrophy, and micrognathia (Figure 2). By cutaneous examination, there were multiple subcutaneous nodules around all fingers, nasal ala, scalp, and nape of the neck of around 0.5-1 cm width. Fleshy nodules were seen in the lower lip of around 5 cm width and involving two-third of the ear lobule bilaterally (Figure 2). There were dusky erythematous plaques on the lower aspect of the back and hips over bony prominences of around 15 cm × 5 cm. Multiple sessile nodules were distributed in the perianal area (Figure 3). The chest, abdomen, and genitalia were clinically free. She has limited joint movement with tenderness and pain, but no redness or hotness was detected. Flexion deformity was present in the back, lower limbs (hip and knee), and both wrists (Figure 4). The ophthalmological examination was normal.

Laboratory investigations showed the following: serum sodium of 139 mmol/l (N: 132-146), potassium of 3.8 mmol/l (N: 3.5-5.5), high chloride of 120 mmol/l (N: 98-107), very low serum bicarbonate of 10 mmol/l (N: 24-32), normal serum anion gap of 12.8 (N: 8-16), in the presence of positive urine anion gap, urine pH of 6, and hypercalciuria as calcium creatinine ratio of 1.4 (N: 0.1-0.7). The diagnosis of distal renal tubular acidosis was established, and the patient was started on NaHCO3. Other biochemical tests comprising urine organic acids, serum amino acids, lysosomal enzymes, urine

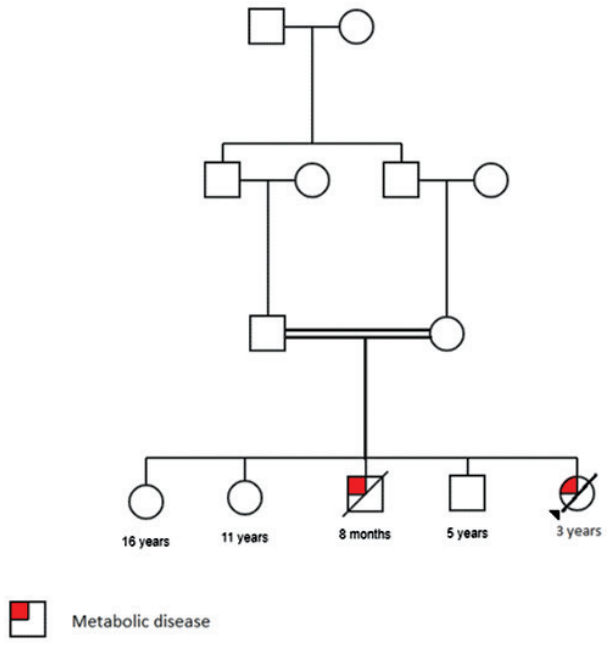

Figure 1. *Pedigree of the patient, parents are consanguineous, a boy sibling died of a similar condition at the age of 8 months, and other three siblings are healthy.*

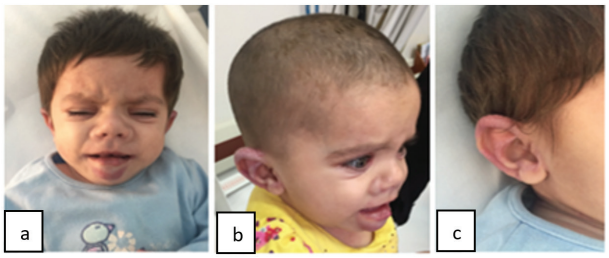

Figure 2. *Facial dysmorphic features: depressed nasal bridge, saddle nose, wide philtrum, micrognathia, and fleshy nodules on lower lips (a,b) fleshy nodules on both ears (c).*

Figure 3. *Joint contracture and flexion deformity of both wrists and lower limbs (hip and knee).*

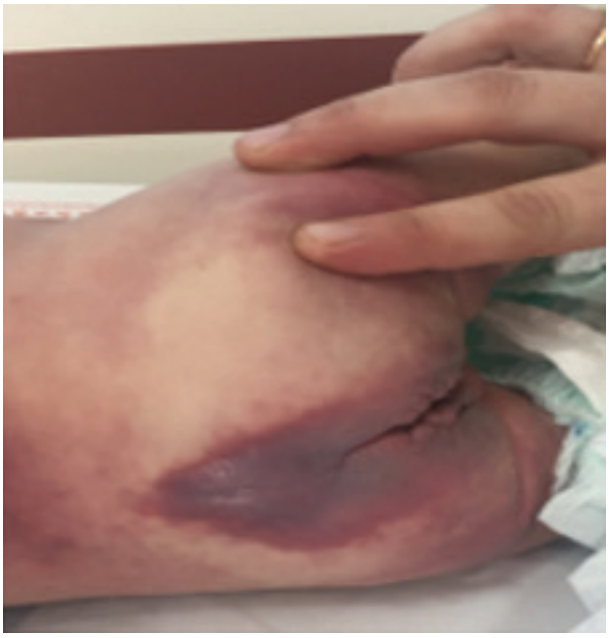

Figure 4. *Dusky erythematous plaques on the lower aspect of back over boney prominences and perianal sessile nodules.*

mucopolysaccharides, oligosaccharides, and sialic acid were normal.

Biopsy was taken, and histopathological examination showed skin lined by focally atrophic epidermis acellular eosinophilic interstitial hyaline material in the dermis. Congo red shows no amyloid deposit, and no atypia is noted. These findings indicated the diagnosis of HFS. The radiological skeletal survey demonstrated generalized demineralization, including the vertebrae and the skull. The right sixth rib showed deformity indicating an old fracture. Lucency in the right tibia and thinning of the cortices of the lower limbs and pelvis were also seen. The abdominal ultrasound showed bilateral renal abnormal areas of calcification, which may suggest multiple calculi/nephrocalcinosis associated with significant urinary bladder sedimentation. MRI brain showed global supratentorial volume loss with *ex vacuo* dilation of the ventricles. Delay in myelination with volume loss affecting the periventricular white matter suggests neurodegenerative disease.

The diagnosis was ultimately confirmed by molecular deoxyribonucleic acid sequencing of *ANTXR2* gene which revealed a homozygous, c.652T>C, p.Cys218Arg, and Chr4 (GRCh37): g.80957171A>G. It has been previously described as disease causing HFS by Hanks et al (4).

The course of the disease was severe and progressive, and the child had recurrent episodes of diarrhea. At 3 years of age, she suffered from diarrhea with severe dehydration with no response to treatment, deterioration of the general condition occurred, and the child passed away.

Discussion

Infantile systemic hyalinosis was first described by Murray in 1873 as "molluscum fibrosum" (2). Although ISH is considered a rare disease, a review of 50 cases was reported worldwide to date. A significant proportion of patients was reported from Arabian countries due to the high rate of consanguinity, with 21 cases reported from Saudi Arabia (7). However, this is the first reported case of ISH from Bahrain. As of yet, almost 34 different pathogenic ANTXR2 mutations have been investigated, including missense, nonsense, and splice-site mutations (8). The majority of ANTRX2 mutations were homozygous.

The mean age of presentation with the disease was described in the previous literature works as 2 months, similar to the patient; however, some cases presented as early as few days of birth or as late as 5 months (2). ISH diagnosis depends on its characteristic physical findings. All the previous literature works shared manifestation of labiogingival hyperplasia, subcutaneous nodules involving the knuckles and malleoli, facial reddish papules involving the ear lobes, nasolabial folds, chin, and mouth, as well as joint contracture involving the metacarpophalangeal joints of the hand, shoulder, elbow, wrist, pelvis, and knee with frog-leg position (9), supporting the case presentation and building a structure of the clinical criteria of the disease. Only few literature works shared the coarse facial features and perianal sessile nodules with this case, and one was described as reminiscent of the Cornelia de Lange's syndrome with marked synophrys. On the other hand, some literature works reported bizarre manifestations, one with rectal prolapse, and two cases with buttocks pressure ulcers (10). Protein enteropathy was reported in most of the literature works as the cause of death, supporting what was found in this case. This patient did not present with skin tumors or intracranial tumors as discussed in some literature works (11). This case is considered severe (grade 3) based on the proposed grading system by Nofal et al. (12). In the reported patients, other than hypochromic microcytic anemia, all laboratory results were normal (13), and there was no previously mentioned renal tubular acidosis, making this case the first to highlight this new manifestation in ISH with biochemical and ultrasound confirmation.

With all of these manifestations, ISH must be differentiated from several genetic conditions. One of them is Farber disease (Farber lipogranulomatosis), which is characterized by periarticular subcutaneous nodules and painful swollen joints. However, cases reported with Farber disease have neurologic manifestations, unlike those with inherited systemic hyalinosis. The other is I-cell disease (mucolipidosis II), which also manifests with coarse facial feature and joint contractures (6).

The management of ISH is palliative. Some authors recommend the early surgical excision of nodules or intralesional steroids to reduce the size of the lesions,

as well as joint contracture capsulotomy, but all these measures showed temporary benefit (14). On the other hand, oral D-penicillamine (9) and interferon-alpha 2b (15) had proven improvement in mobility, but the latter awaits confirmation. In this case, the patient was evaluated for protein-losing enteropathy, and fluid hydration and nutritional supplementation were instituted accordingly.

The patient died at the age of 3 years, as it was concluded from literature works that the affected patients usually die at the age of 11-39 months due to pneumonia or diarrhea (6). However, atypical prolonged survival was noted in a case from Egypt who died at the age of 4½ years as a complication of anesthesia (10).

Conclusion

While the clinical outcome of the disease is poor without curative treatment, establishing an early diagnosis of ISH, beginning with clinical suspicion to molecular analysis, is essential for accurate management and carrier and risk assessment of family members

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List of Abbreviations

HFS	Hyaline fibromatosis syndrome
ISH	Infantile systemic hyalinosis
JHF	Juvenile hyaline fibromatosis

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The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at the institution to publish an anonymous case report.

Consent for publication
Written consent was obtained from the parents of the subject to publish this case report and publish the pictures of the subject.

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