Case Report

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Infantile systemic hyalinosis: Report of two severe cases from Saudi Arabia and review of the literature

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Summary **Infantile systemic hyalinosis (ISH) (OMIM 228600) is a rare fatal autosomal recessive disorder characterized by extensive deposition of hyaline material in many tissues. Consanguinity has been recorded in many cases. Herein we present two new Saudi cases with review of the literature. Our first proband was a 9 month-old male who was the first baby for parents descended from a closed consanguineous pedigree. The second proband was a 13 month-old male who was the first baby for consanguineous parents (3rd C). Both cases presented with bilateral painful limited limb movement with joints contractures, low birth weight (< P5), severe generalized stiff skin, hyper-pigmented skin over bony prominences, fleshy perianal masses and gingival hypertrophy. The first child died at 18th month as a result of recurrent chest infections. The second proband showed a severe progressive course of joint contractures, and died at 19th month because of failure to thrive and recurrent infections. Although the clinical features of ISH are characteristic, the disease is under/miss diagnosed. The role of consanguinity needed to be highlighted to the community. Careful clinical examination and molecular diagnosis will be helpful for genetic counseling, prenatal diagnosis and early treatment.**

Keywords: Hyalinosis, AL Madinah, consanguinity

1. Introduction

Infantile systemic hyalinosis (ISH) (OMIM 228600) is a very rare fatal autosomal recessive disorder of connective tissue belonging to the heterogeneous group of genetic fibromatosis (*1*). Both males and females are equally affected. The disease presented usually at birth or within the first few months of life with progressive painful joint contractures, skin hyperpigmentation over bony prominences, and papules on the face, scalp, and neck (*2*).

Other notable characteristic features are gingival hypertrophy and thickened skin. However, the children with ISH are found to be intellectually normal. Affected children suffer from osteopenia which results in increased susceptibility to bone fractures. Intractable diarrhea as a result of protein loss enteropathy and/or recurrent infections are commonly reported in children suffering from ISH. Because of multisystem failure resulting from complicacy, many patients die in infancy (*3,4*).

The disease was first called Molluscum Fibrosum by Murray in 1873 (*5*) then Juvenile Hyaline Fibromatosis (JHF) and ISH. (Drescher *et al*., 1967; Landing and Nadorra, 1986) (*2,6*). Due to similarity of the clinical features of both JHF and ISH, the Hyaline Fibromatosis (HF) term was used by some authors. ISH could be differentiated from JHF by its severe phenotype. About 150 cases have been reported in the literature without notable ethnic or geographic predisposition (*7*).

Histologically ISH is characterized by deposition of hyalinized fibrous material (glassy translucent substance of glycolprotein) in many tissues like skin, skeletal muscle, cardiac muscle, gastrointestinal tract, lymph nodes, spleen, thyroid, and adrenal glands (*8*).

Capillary morphogenesis gene 2 - capillary morphogenesis protein 2 (*CMG2*)/Anthrax Toxin Receptor 2 (*ANTXR2*) - mapped to chromosome 4q21.21, was identified as the gene responsible for these two rare autosomal recessive human genetic disorders, ISH, (MIM

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236490) and JHF, (MIM 228600) (*7,9*).

Type I membrane protein, which is universally expressed in all human tissues, with exception of the brain, is encoded by the *CMG2* gene (*10*). Scobie *et al*., 2003 reported *CMG2* as the subsequent receptor for the anthrax toxin, hence its certified name of *ANTXR2*. Almost 34 different mutations have been investigated, predominantly in exons and spread from exon 1 to exon 15. Although most reported mutations have been identified only once, there is a mutational hotspot at position (1074-1077) in exon 13 where insertion or deletion of one or two bases has been described (*7,10*).

Non-cancerous tissue proliferation and nodules are the most outstanding external features found for all patients and are the hallmark of the disease. These nodules are not seen at birth but may develop in the first month of life. Since those nodules develop over areas of mechanical stress, upregulation of microtrauma repair mechanisms might be the suggested pathogenesis (*11*). The nodules were found to be rather cellular at the onset, while older ones contained mainly extra cellular matrix (*12,13*).

Currently the diagnosis of ISH is based on clinical data but molecular genetic testing is available on a research basis only. Treatment of ISH is palliative as physical therapy and nutritional support improve the quality of life of the patients (*14*).

In this report we present two new Saudi cases from Almadinah Almonwarh province referred to us for genetic evaluation during our work in Taibah University from September 2013 to September 2014. These two cases were of interest because of closed consanguineous pedigree, severe course of the disease, huge popular-nodules at the perianal region, generalized joint contractures, failure to thrive and death before 2 years of age. We aimed to present a fine characterization of the phenotype of ISH in order to facilitate early diagnosis of cases, which are very important for genetic counseling and early treatment.

2. Case 1

A 9-month old male child who was the first baby of an apparently healthy young couple descended from a closed consanguineous pedigree (Figure 1) was referred for a medical genetics consultation. The family history was negative for birth defects and genetic disorders except for primary infertility. He was a full term baby born by vaginal delivery after induction. Pregnancy was complicated with threatened abortion during the first trimester that was treated with hormonal therapy. Reduced and weak intrauterine fetal movement was noticed by his mother. Prenatal ultrasound examination at 36 weeks of gestation showed small sized baby with normal amount of amniotic fluid.

At birth, his weight was 1,300g (less than 5th percentile). His cry was delayed with limited painful limb movement bilaterally. Within the first three months of life, parents noticed progressive limb contractures with limitation of joint movements of the four limbs and pain on minimal handling together with obvious perianal masses.

Genetic examination was done at 9th month of age, his height was difficult to be measured due to severe joint contractures, weight was 5 kg (less than 5th Percentile), and head circumference was between 10th and 25th percentile. Weak cry and irritability was noticed with high sensitivity and excessive crying on passive movement of his limbs. Failure to thrive and delayed motor milestones like neck support and sitting were diagnosed.

Craniofacial examination revealed minimal coarse faces like broad forehead, down slanting palpebral

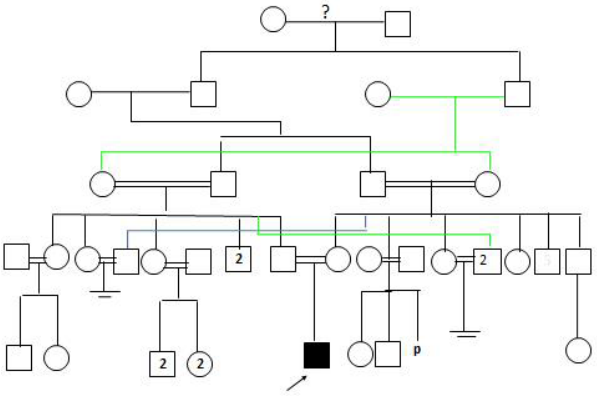

Figure 1. Pedigree of the studied family of the first case: three generations were studied from both parents. Close consanguinity and primary infertility on both paternal and maternal side were noted. P: current pregnancy at the time of the study.

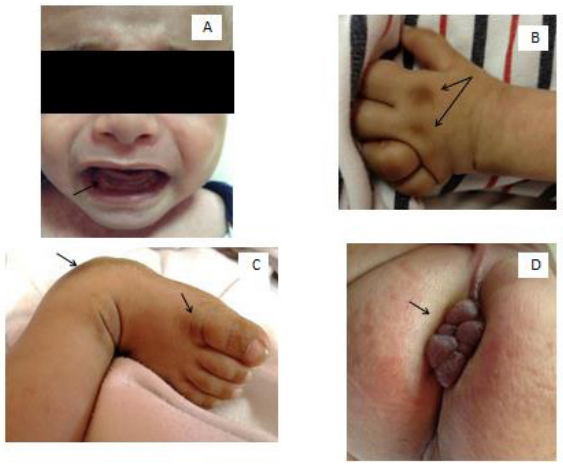

Figure 2. Clinical features of case 1. (A) Gingival hypertrophy with delayed teeth eruption. **(B)** Skin overlying metacarpophalangeal and proximal phalangeal joints was shiny, hyperpigmented and thickened. Contractures of metacarpophalangeal and interphalangeal joints. **(C)** Both feet showed marked contractures of metacarpophalangeal joints, dorsiflexion, skin hyperpigmentation. Heel skin is thickened and hyperpigmented. **(D)** Giant papular perianal nodules.

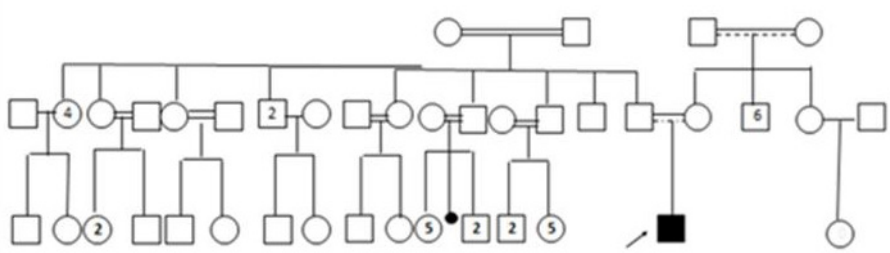

Figure 3. Pedigree of the studied family of the second case. The parents were third cousin relatives and close consanguinity was manifested on the paternal side.

fissures, depressed nasal bridge, low set ears and gingival hypertrophy. By cutaneous examination, his skin was thick and shiny showing hyperpigmentation over bony prominences like malleoli and knuckles of upper and lower limbs but there were no focal nodules and/or papules. Limited joint movement with tenderness and pain with no redness or hotness was seen. Flexion deformity was present at elbows, wrists, knees, ankles and small joints of both hands (Figure 2).

Chest, abdomen and genitalia were clinically free. By inspection, fleshy perianal nodules were seen. Hematological and biochemical investigations were normal. Lysosomal storage diseases were excluded by MS/LS analysis and chromosomal malformation syndrome was absent as shown by normal male karyotype (46, XY).

Radiological skeletal survey demonstrated generalized osteopenia with bilateral periosteal reaction of radii, ulnae, tibia and fibulae. MRI brain showed slight prominence of ventricular system and cortical sulci. Abdominal ultrasound and computerized tomography (CT) screening organs were normal. Ophthalmological examination was normal.

The course of the disease was severe and progressive, and the child had recurrent episodes of pneumonia. At 18th month he suffered from pneumonia with no response to treatment, deterioration of the general condition occurred and the child passed away.

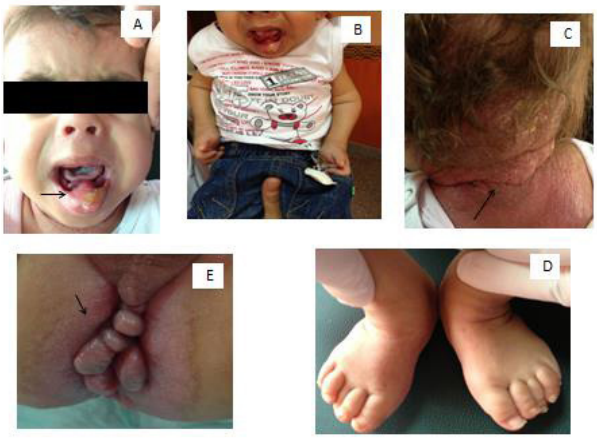

Figure 4. Clinical features of case 2. (A) Marked gingival hypertrophy with normal pink firm gingival tissue which almost covered erupting teeth. The lower lip is everted due to prominent gingival mass. **(B)** Contractures and flexion deformity at both elbow joints. **(C)** Severe eczematous papules and nodules in the auricular area and neck. **(D)** dorsiflexion of foot with hyperpigmented skin patches over heels. **(E)** Large papular perianal nodules and severe eczema in perianal area.

3. Case 2

A full term male baby who was the first child of an healthy consanguineous couple, a mother aged 23 years and the father was 28 years (3rd Cousins) (Figure 3). The family history was negative for similar conditions or any genetic disorders. Pregnancy course was normal except for reduced fetal movement. Prenatal follow up ultrasound showed normal amniotic fluid. Labor was induced at 40th month of gestation by caesarian section due to fetal bradycardia.

Birth weight was 3,000 g with a weak cry, the baby was stable and discharged from the hospital. Few days later, the mother noticed painful limited limb movement had started on the right upper limb then limited mobility became bilateral and involved the four limbs with severe pain on handling. The child was admitted to the hospital for clinical evaluation. Laboratory investigations were normal and CT brain was unremarkable. Perianal masses were observed by the parents at 9th month of age and oral mass appeared at the first year.

Genetic examination was done at 13th month of age, his height was 62 cm with joint contractures, his weight was less than 5th percentile (7.5 kg), head circumference was 47 cm. his motor milestones were delayed.

Craniofacial examination revealed broad forehead, down slanting palpebral fissures, depressed nasal bridge, low set ears and gingival hypertrophy with a marked central swelling extended deep in the bottom of the tongue. On cutaneous examination, skin was of normal texture with normal hair distribution. Hyperpigmentation over bony prominences like malleoli and knuckles was seen, with no focal nodules and/or papules. Severe eczema around the neck and in napkin area was present. Limited joint movement with pain and tenderness in all extremities was seen, and there were no redness or hotness and flexion deformity present at elbows, wrists, knees, ankles and small joints of both hands (Figure 4). Chest, abdomen and genitalia were clinically free. By

inspection, large fleshy perianal nodules were seen.

Radiological skeletal survey demonstrated generalized osteopenia with bilateral periosteal reaction. CT brain was normal with wide extra-axial CSF places. Abdomenal ultrasound was normal with no organomegally and ophthalmological examination was normal. The case had normal enzymatic studies for various lysosomal storage diseases. Chromosomal analysis of this case showed normal male karyotype (46, XY).

The general condition was deteriorating and the child died at 19th month of age because of failure to thrive and recurrent chest infections.

4. Discussion

ISH and JHF shares many clinical resemblances, both are caused by mutations in the *CMG2/ANTXR2* gene. Both syndromes are characterized by gingival hypertrophy, bilateral generalized joint contractures, and subcutaneous and perianal fleshy nodules. A progressive severe course, an earlier onset and death in early childhood characterize ISH. They share characteristic histological similarities (*15*).

Since ISH is rare it is difficult to diagnose, and it should be differentially diagnosed very carefully from other diseases that present with chronic pain, subcutaneous nodules, multiple malformations and joint contractures.

Chronic pain and joint contractures in infancy have very limited differential diagnosis. The most important one is lysosomal storage diseases (LSD). ISH may have some resemblance to LSD. The two studied patients herein had normal enzymatic studies for various LSD including, Farber disease (Farber lipogranulomatosis) [OMIM 228000] which presents with skin nodules over joints, painful movement and diminished cognitive function. On the contrary ISH child is cognitively normal. Also in ISH the abnormal hyaline material is deposited extracellularly in the dermis, while in LSD it is accumulated intracellularly. Hematoxylin and eosin staining of skin biopsy from perianal papular-nodules, in both cases, showed normal epidermis with deposits of hyaline material throughout the papillary dermis.

The abnormal physical findings seen in ISH might suggest conventional cytogenetic analysis to rule out multiple malformations. In our studied cases, normal karyotypes have been documented. Multiple large sized perianal nodules/papules were found in both studied cases. Other authors reported perianal nodules/papules but our cases had marked large sized nodules (*16,17*). The perianal nodule, although it is highly characteristic of ISH, might be misdiagnosed as condylomata which herein has been ruled out by a negative test for human papilloma virus (*18*).

Marked gingival hyperplasia, results in difficulties in suction, mastication and leads to malnutrition, and has been reported earlier as in our cases (*19*).

Almost all characteristic clinical features of ISH, such as gingival hyperplasia, limited painful joint contractures, diffuse, thickened skin, hyperpigmented plaques on bony prominences, perianal fleshy nodules, frequent severe infections, and fatal outcome, were detected in our probands.

Malnutrition due to feeding problems, perioral stiffness, difficult mastication, and protein-losing enteropathy due to thickening and hyaline infiltration of the intestinal walls were noted in both cases. These finding were the main causes of growth retardation and failure to thrive.

Laboratory investigations showed low levels of serum IgG, protein, albumin and hemoglobin in both cases. In the literature some cases have similar laboratory abnormalities, and others have not (*11,19*).

Both cases suffer from recurrent respiratory problems, which might be related to hyaline deposits in the lungs. The same findings have been previously reported in the literature (*20*).

Although ISH is considered a rare disease, a review of 19 cases were reported from a referral center in Saudi Arabia in 2005. While ISH was reported globally and in all ethnic groups, many cases reported from Arabian countries are due to a high rate of consanguinity (*21-24*). In Saudi Arabia there are high consanguinity rates (25-60% of all marriages are consanguineous), and particularly the practice of first cousin marriages. In some areas (like Al Madina) the society is still tribal. Tribal groups and families descending from restricted ancestors may accumulate genetic and congenital diseases (*25*). Further detailed genetic studies might help to elucidate this issue.

It has been reported that ISH has a very poor prognosis since it results in death within the first two years of life (*2,25,26*). Both studied cases died by the age of two years due to recurrent respiratory infections.

Up to date there is no known specific treatment for ISH, only nutritional support and physiotherapy could improve the child's quality of life.

5. Conclusion

Clear guidelines are needed for early, correct diagnosis of the disease. Clinical data and detailed analysis of genetic *CMG2/ANTXR2* mutations will lead to better understanding of the disease pathogenesis, which may in turn help to reduce the high morbidity and mortality associated with ISH. These data provide the basis for diagnostic testing and genetic counseling for families of affected cases.

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