Case Report

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Infantile systemic hyalinosis in identical twins

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Summary **Infantile systemic hyalinosis (ISH) is a rare disorder belonging to the heterogeneous group of genetic fibromatoses. It is a rare, progressive, fatal autosomal recessive condition characterized by widespread deposition of hyaline material in many tissues caused by mutations in the anthrax toxin receptor 2 gene - ANTXR2. It presents hyperpigmented skin over bony prominences. Characteristic purplish patches develop over the medial and lateral malleoli of the ankles, the metacarpophalangeal joints, spine and elbows, with progressive joint contractures, osteopenia, skin abnormalities and chronic severe pain. The present case reports the occurrence of infantile systemic hyalinosis in twin brothers five months of age who had come for early intervention for joint contractures representing characteristic brownish patches over bony prominences. ISH cases reported until this date have been less than 20 and the present case is unique in nature since this is the first time ISH is reported in twins globally and the symptoms have been identified at an early age.**

Keywords: Infantile systemic hyalinosis, Hyalinosis, Mutation in ANTRX2

1. Introduction

Infantile systemic hyalinosis (ISH) is a rare disorder of genetic fibromatoses which is a fatal, autosomal recessive disorder with deposition of hyaline material in many tissues (*1*). ISH (severe form) is a part of hyaline fibromatosis syndrome and must be differentiated from juvenile hyaline fibromatosis (mild) as both belong to hyaline fibromatosis syndrome and recent data indicate that both severe and mild forms of inherited systemic hyalinosis are caused by mutations in ANTXR2/CMG 2 (capillary morphogenesis gene 2) (*2-4*).

Infantile systemic hyalinosis presents hyperpigmented skin over bony prominences, characteristic purplish patches develop over the medial and lateral malleoli of the ankles, the metacarpophalangeal joints, spine and elbows (*5*), with progressive joint contractures, osteopenia, skin abnormalities, chronic severe pain and widespread deposition of hyaline material in many tissues such as the skin, skeletal muscle, cardiac muscle, gastrointestinal tract, lymph nodes, spleen, thyroid and adrenal glands (*6,7*).

Clinical features are evident either at birth or within the first six months of life. Small pearly papules (predominantly on the face, scalp, and neck), massive gingival hypertrophy, and fleshy nodules in the perianal region are the dermal lesions found in ISH (*2,3*). Excessive crying and severe pain on passive movement is common. A depressed nasal bridge, variable ear malformations and a slightly coarse facial appearance may be present. Death occurs secondary to sepsis with renal, respiratory and heart failure, usually by the age of two years due to intractable diarrhea (*7-9*). The survival age may vary from 2-6 years based on management with nutritional supplementation, physiotherapy for joint contracture, use of NSAIDS and oral rehydration therapy and antibiotics for diarrhea.

2. Case Report

The present case is about identical twins 5 month old baby boys, who have come for early intervention and treatment for relieving joint contractures (Figure 1A). When they were two months old, they were confirmed as victims of infantile systemic hyalinosis by a genetician. They were offspring of third degree

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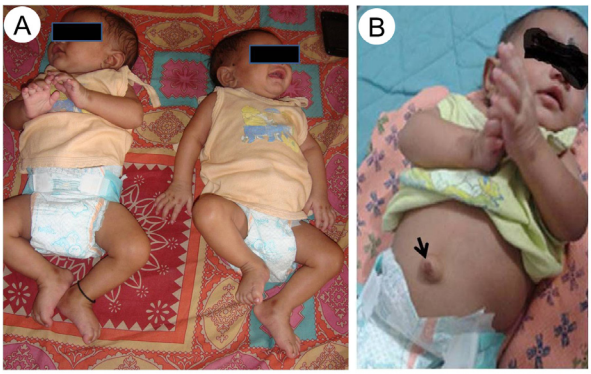

Figure 1. Image of infantile hyalinosis in identical twins. (A) showing the contractures at knee joints; **(B)** showing umbilical hernia in one of the twins (Arrow mark).

Figure 2. Image of infantile hyalinosis in identical twins. Showing the purplish patches over metacarpophalangeal joints characteristic of hyalinosis.

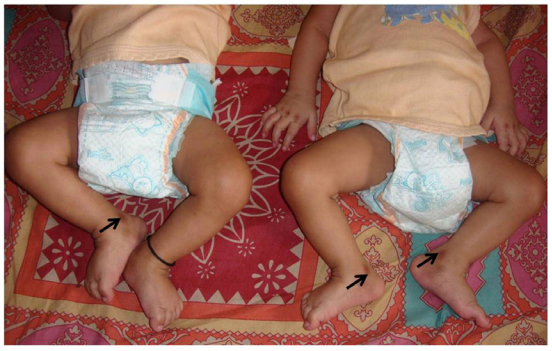

Figure 3. Image of infantile hyalinosis in identical twins. Showing purplish patches development over the medial malleoli (Arrow marks) of the ankles.

parents whose grand fathers are brothers. The mother of the children who is of 21 years old conceived at 19 years and her first pregnancy was medically terminated in her third month because of detection of congenital malformations identified through ultrasonography. After one and half years she delivered full term monozygotic twin baby boys, sharing a single placenta, by caesarian section. Mother was diagnosed as hypothyroid earlier and she was on medication for this condition.

One of the baby boys was 200 grams less in weight at birth, weak when compared to the other and later maintained a 500 gram difference in weight. The parents on detailed enquiry informed us that both baby boys started crying continuously and had disturbed sleep. When they try to lift them or during bathing or dressing, the twins were crying and the one who is weak had more problems at the shoulder girdle. Both of them had a mild umbilical hernia, whenever they cried the loop herniated prominently (Figure 1B). By the second month parents noticed joint contractures and the boys were treated with vitamin D with no success. They presented typical flexion at elbow and extension at wrist and arms in a pronated position. They failed to do supination even on trials. Later they consulted a genetician who diagnosed them as ISH by presence of joint contractures and purplish patches over malleoli and wrist. Characteristic purplish patches increased over the medial and lateral malleoli of the ankles and developed over the metacarpophalangeal joints by the third month (Figures 2 and 3). Contractures were progressive and extremities became fixed with the hips and knees in flexed position as indicated in radiographs and the ankles in dorsiflexion. Both developed diarrhea of unknown etiology by five months for ten days and were treated with antibiotics and oral rehydration therapy by a pediatrician. By the sixth month they developed reddishness on the face whenever they cried and also suffered from recurrent diarrhea. The baby boy with less weight started developing fleshy nodules in the perianal region as well as on the face by 8 months, whereas the elder one had nodules which appeared first on the face by 8 months and perianal region by 11 months. Craniofacial dysmorphism exhibited by ISH was not observed in them. Gingival hypertrophy characteristic of ISH appeared in them by 11 months of age (Figure 4 A-F). They presented with delayed developmental milestones in motor activities as well as in speech. Both babies have continuous recurrence of diarrhea. Polymerase chain reaction and Sanger sequencing covering all exon – intron boundaries of the *ANTXR2* gene was carried out in blood samples to find the mutation. BLAST analysis was done to check for any pathogenic variation. This test revealed the sample is homozygous for insertion mutation c.277_278insATTATTT (or p.L93Yfs*14) in exon 3, leading to premature termination of protein.

3. Discussion

The present case of identical twins exhibits all the characteristic features of ISH *in toto*. Infantile systemic hyalinosis is a condition characterized by widespread deposition of hyaline material in many tissues. Infantile systemic hyalinosis presents hyperpigmented skin over bony prominences with progressive joint contractures, osteopenia, massive gingival hypertrophy, skin abnormalities, severe chronic pain, widespread deposition of hyaline material in many tissues and

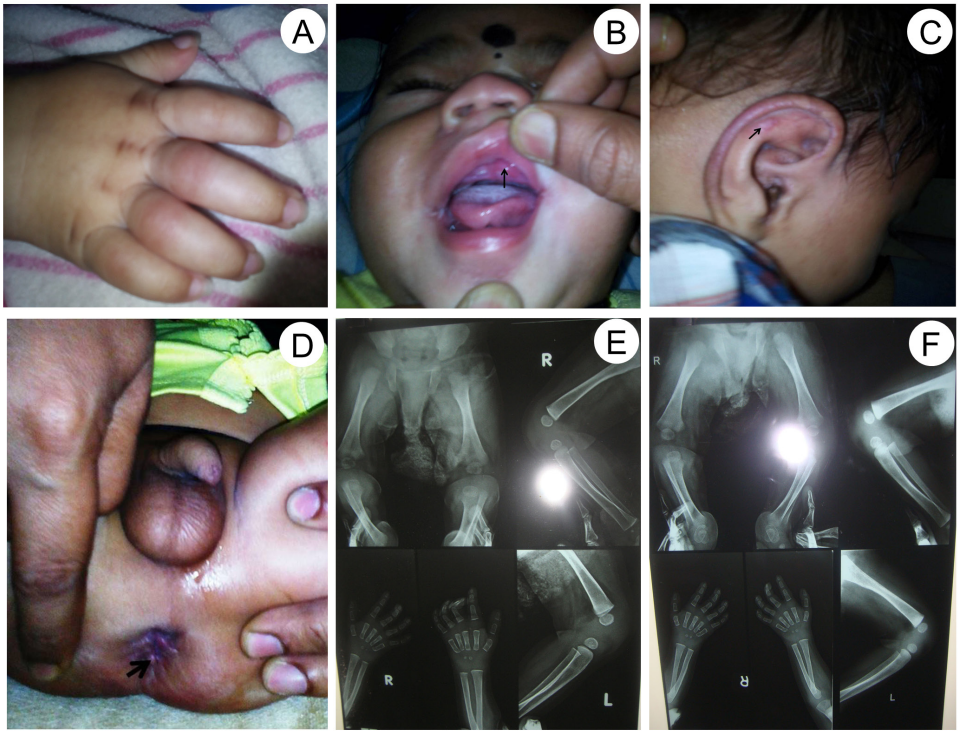

Figure 4 Images of different regions affected in infantile hyalinosis in identical twins. (A) showing Progression of joint contractures in the hand; **(B)** showing Gingival hypertrophy (Arrow mark); **(C)** showing Reddishness and papule over earlobe (Arrow mark); **(D)** showing Papular nodules in the perianal region (Arrow mark); **(E)** & **(F)** radiographs showing the joint contracture.

small pearly papules on face, and perianal regions. Survival beyond 3-4 years of life may become difficult because of impaired chest wall movement, malnutrition, protein losing enteropathy, osteopenia, intractable diarrhea and sepsis involving multi organ systems. Recent investigations documented the use of d-pencillamine has an inhibitory effect on abnormal collagen maturation and shows some improvement in joint mobility (*10*).

The gene responsible for hyalinosis is chromosome 4q21.21 and deletion mutations in the *ANTXR2* gene (anthrax toxin receptor 2 gene) or *CMG2* (capillary morphogenesis protein gene 2) gene cause infantile systemic hyalinosis (*2,3,9*). *TheANTXR2* gene provides instructions for making a protein involved in the formation of tiny blood vessels (capillaries) and is also important for maintaining the structure of basement membranes, which are thin, sheet-like structures that separate and support cells in many tissues. In ISH the defective synthesis of glycosaminoglycans which results in the abnormalities in collagen synthesis and in the *CMG2* gene that binds to type 4 collagen and laminins which provide strength to the basement membrane (*11,12*). The accumulation of an abnormal collagen in different parts of the body is seen in ISH which is responsible for the symptoms. Mutations in the *ANTXR2* gene disrupt the formation of basement membranes, allowing the hyaline substance to leak through and build up in various body tissues (*13*). This condition is inherited in an autosomal recessive pattern, and the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but typically do not show signs and symptoms of the condition.

ISH has to be differentially diagnosed with Farber's disease (*14*), I- cell disease which is a storage disorder (*12*), Stiff skin syndrome (*15*), Winchester syndrome (*16*), Pseudo-Hurler polydystrophy, Lipoid proteinosis and Caffey disease (*17*), and congenital generalized fibromatosis (*18*).

The present case is diagnosed as ISH because it reveals all of the symptoms which are characteristic of ISH and it was ruled out to be any of the above mentioned diseases because of its completion of characteristic symptoms.

ISH can be confirmed by demonstration of hyaline material in the dermis by light microscopy with PAS stain and electron microscopy which reveals cells filled with fine fibrillary material with an enlarged endoplasmic reticulum and golgi apparatus (*19*) also, by intestinal biopsy which reveals villous atrophy, edema, lymphangiectasia, and hyalinosis, and molecular genetic testing for gene *ANTXR2* (*17*). Further, sequencing of the *ANTXR2* gene carried out in blood samples of the present study confirms the clinical diagnosis of infantile hyalinosis. This test has revealed the sample was homozygous for insertion mutation c.277_278insATTATTT (or p.L93Yfs*14) in exon 3, leading to premature termination of protein.

Management of ISH can be done by initial diagnosis,

followed by nutritional, immune and intestinal malabsorption evaluation and echocardiogram evaluation because the heart is involved, to increase life span and prevent recurrence of infections.

To conclude the present case of twins exhibiting infantile systemic hyalinosis is a rare and uncommon genetic disorder of third degree parents confirmed as victims of ISH and not responding well to treatment compared to normal infants. This being the first case of ISH in India planning therapeutic strategies is difficult for pediatricians and other physicians. Hence awareness has to be raised to mutation in the *ANTXR2* gene by explaining the risk of recurrence in future siblings being 25%. Prenatal diagnosis is possible by fetal DNA analysis at around 12 to 16 weeks of pregnancy. Knowledge regarding ISH needs to be updated by clinicians. This is the first case of ISH reported in identical male twins to the best of our knowledge.

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