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Case report:

Infantile Systemic Hyalinosis

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Abstract:
This case report represents an infant who presented with typical clinical and biochemical features of ISH with a progressive and disabling joint pain and contractures leading to eventual death at age the of 6 months from severe chest infection and diarrhea.ISH is a rare autosomal recessive disease that involves deposition of hyaline material in multiple tissues throughout the body, resulting in joint contractures, subcutaneous nodules, diarrhea, and growth failure.ISH typically presents between birth and 6 months of age. It is equally common in males and females. While described in many ethnic groups, it has most commonly been seen in children of Turkish, Indian, and Moroccan descent. ISH being autosomal recessive disorder, awareness has to be raised to 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. To conclude, the prognosis of ISH is poor and most treatments have not proved beneficial. Physical therapy and nutritional support may improve quality of life. Awareness and early diagnosis of the disease, recognition that joint contractures are painful, and control of pain will lead to decreased invasive testing and increased patient comfort. Correct diagnosis of disease using clinical findings and genetics studies are important for family planning and counseling.
Keywords: Infantile Systemic Hyalinosis , autosomal recessive disorder

Introduction:

Infantile systemic hyalinosis is a rare, progressive, fatal autosomal recessive disorder (1).It is characterized by extensive deposition of hyaline in various tissues like skin, gastrointestinal tract, cardiac muscle, skeletal muscles, lymph nodes, spleen, thyroid, and adrenal glands (2).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.

Osteopenia, bone fractures, short stature, persistent diarrhea with protein losing enteropathy (PLE) due to intestinal lymphangiectasia (IL), increased susceptibility to infections and failure to thrive are the main systemic manifestations.

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 ISH.

Currently the diagnosis of ISH is based on clinical data and skin biopsy. Molecular genetic testing is available only in a few centres only.

Case report:

A 5month,10 days old male baby third order born to a non consanguineous parents was brought with complaints of persistent diarrhea since 4 months and hyperpigmented nodules over the joints associated with shiny skin and restriction of movement and excessive crying when holding the child and with movement of limbs. The child was admitted with similar

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complaints previously where he was treated symptomatically for diarrhea and recurrent respiratory tract infections and was advised physiotherapy for joint contractures.

The baby was born full term by lower segment caesarian section and weighed 2.2 kg. There was history of oligohydramnios.There was no history of perinatal hypoxia. Postnatal period was uneventful. As per mother's history gross motor and fine motor milestones delayed but social and language milestones were achieved. On examination baby was irritable, afebrile,vitally stable with no signs of dehydration. The baby had gum hypertrophy. He had shiny, hyperpigmented nodules over the bilateral metacarpophalangeal joints, wrist joint,knee joint, medial malleolus with contractures of the joints with restriction of range of movements. There was tenderness at shoulder, elbow, hip, knee, ankle and interphalangeal joints.

On further investigations hemogram revealed leucocytosis and thrombocytosis.Liver function tests were normal except serum proteins decreased. Kidney function tests were within normal range. There was hypocalcemia.C reactive protein was positive. Thyroid tests were normal..Stool microscopic examination was normal. Antinuclear antigen test was negative .Ultrasonography of abdomen and pelvis showed mild circumferential thickening of descending and sigmoid colon.USG of hip, knee and wrist joints was suggestive of subcutaneous soft tissue swelling.MRI Brain showed thinning of corpus callosum. With history of painful nodules and persistent diarrhea with failure to thrive, ISH was suspected and clinical exom sequencing test was advised. Hotspot mutation analysis for ANTXR2 gene was done. The result suggested that the baby was homozygous for the known pathogenic mutation c.1072_1073insC:p.A359Cfs*13 in ANTXR2 gene. The baby was managed conservatively with supportive care given with pain relief, antimicrobial therapy, and dietary modifications. The parents have been counseled regarding the disease and poor prognosis associated with the disease. Unfortunately, the baby died at the age of 6 months.

Discussion:

This case report represents an infant who presented with typical clinical and biochemical features of ISH with a progressive and disabling joint pain and contractures leading to eventual death at age the of 6 months from severe chest infection and diarrhea.ISH is a rare autosomal recessive disease that involves deposition of hyaline material in multiple tissues throughout the body, resulting in joint contractures, subcutaneous nodules, diarrhea, and growth failure.ISH typically presents between birth and 6 months of age(6). It is equally common in males and females. While described in many ethnic groups, it has most commonly been seen in children of Turkish, Indian, and Moroccan descent (6).

Clinical features of ISH and the present case:

Features	ISH	Our Case
Papular skin lesions	+	+
Thinckened skin	+	+
Gingival hyperplasia	+	+
Perianal nodules	+	+
Hyperpigmented plaques	+	-
Joint contractures	+	+
Osteoporosis/osteopenia	+	-
Osteolysis	+	-
Persistent diarrhea	+	+
Recurrent infections	+	+
Visceral involvement	+	+
Short stature	+	-

ISH is an autosomal recessive disorder caused by homozygous or compound heterozygous mutations in the anthrax toxin receptor gene (ANTXR2), also called the capillary morphogenesis protein 2 gene (CMG2), located on chromosome 4, long arm, band 21. CMG2 is a type 1 transmembrane protein. In skin and connective tissues, CMG2 binds to type IV collagen and laminins, and is considered a factor to basement membrane strength(7).These data implicate CMG2 in basement-membrane matrix assembly and endothelial cell morphogenesis and suggest that the hyaline material deposited between the endothelial cells and pericytes in ISH and JHF may result from leakage of plasma components through the basement membrane to the perivascular space.Several studies have been published that clinically distinguish between ISH and JHF but note the considerable overlap between the two

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conditions(8,9) in accord with the molecular evidence which now defines their shared genetic etiology(10,11).

Joint contractures, papular and nodular skin lesions, gingival hyperplasia, osteopenia, and normal brain development are clinical features of both ISH and JHF. Patients with ISH present within the first 6 months of life and typically die of infection or diarrhea by 2 years of age, while patients with JHF present later in infancy/childhood with milder symptoms and usually live to the second or third decade(8).Common distinguishing features of ISH include thickened skin, erythema or hyperpigmentation over bony prominences, visceral involvement, persistent diarrhea, frequent severe infections, and failure to thrive. Patients with JHF, on the other hand, tend to have larger nodules, commonly located on the scalp. Preliminary genotype–phenotype analyses in both studies suggested that missense, truncating, and frameshift mutations were associated with a severe phenotype (ISH), whereas in-frame and missense mutations affecting the cytoplasmic domain were associated with a milder phenotype (JHF).Also, there are few disease entities that, mimic the clinical features of ISH, are associated with the early onset of joint contractures including syndromes associated with arthrogryposis such Faber and Winchester and inflammatory connective tissue disorders, namely neonatal onset multisystemic inflammatory disease (NOMID).

Early diagnosis requires clinical suspicion and is important to reduce hospital stay and unhelpful and potentially painful workup and treatments.Treatment of patients with ISH primarily involves supportive care, including pain management with nonsteroidal anti-inflammatory medications and opiates, and physical therapy as tolerated. Oral penicillamine has reportedly improved joint mobility in a few cases but overall has had limited success.

Conclusion:

ISH being autosomal recessive disorder, awareness has to be raised to 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. To conclude, the prognosis of ISH is poor and most treatments have not proved beneficial. Physical therapy and nutritional support may improve quality of life. Awareness and early diagnosis of the disease, recognition that joint contractures are painful, and control of pain will lead to decreased invasive testing and increased patient comfort. Correct diagnosis of disease using clinical findings and genetics studies are important for family planning and counseling.

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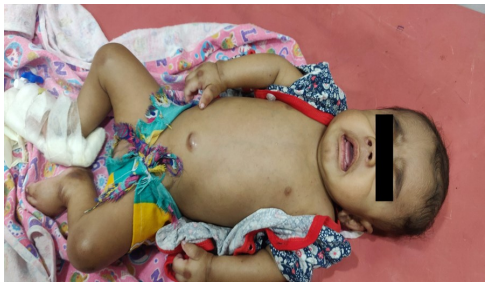
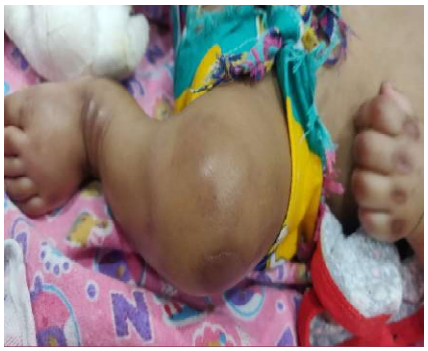
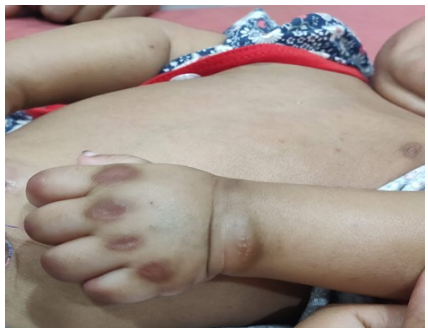
Photograph 1 : Infant with Hylinosis



Photograph 2:Infant with Hylinosis skin showing papules





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