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Case Report

A rare case of infantile systemic hyalinosis: Clinical, histopathological, and genetic insights

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Abstract

Infantile systemic hyalinosis (ISH) is a very rare autosomal recessive disorder with histopathologic hallmark of diffuse deposition of hyaline in connective tissues, leading to its varied clinical manifestations and poor prognosis. We report a case of a 5-month-old boy, born as second child to third degree consanguineous parents, who presented with painful joint contractures, and skin hyperpigmentation. Skin biopsy showed amorphous hyaline deposits, and clinical exome sequencing result came as *ANTXR2* mutation ,in homozygous state confirming the diagnosis. This case report discussthe clinical features , with a special focus on its histopathological and genetic underpinnings. This report adds to the scant literature on ISH, highlighting the significance of genetic testing for exact diagnosis and the necessity for novel treatment approaches.

Keywords: Infantile systemic hyalinosis, Hyaline deposition, Joint contracture, Skin nodule

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1. Introduction

Infantile systemic hyalinosis (ISH) is an uncommon autosomal recessive condition resulting from mutations in the *ANTXR2* gene, which causes widespread hyaline deposition in connective tissues.[1] It usually manifest in the initial months of life with painful joint stifness, skin nodules, gingival hypertrophy , failure to thrive, and recurrent infections, often leading to death by age 2 years.[2] The condition is part of the hyaline fibromatosis syndrome spectrum.

Two types of the disease spectrum are recognized in the medical literature: ISH and JHF.Juvenile hyaline fibromatosis represent a milder disease.[3] ISH is distinguished by an earlier onset, more progressive and severe course, and death in early childhood.[4] Recent studies show mutations in the capillary morphogenesis protein 2 (GMC2) causative of both JHF and ISH.[5] ISH has a higher prevalence in Middle Eastern and North African populations, often linked to consanguinity.[6] This case report describes a 5-month-old male with ISH, confirmed by a novel *ANTXR2* mutation, and provides a comprehensive review of its clinical, histopathological, and genetic features.

2. Case Presentation

A 5-month-old boy, born out of consanguineous marriage, third degree relatives, presented to our tertiary care center with a history of progressive painful joint stiffness, hyperpigmented skin lesions, and failure to thrive. This was their second child with a normal elder sibling. The family history was unremarkable for genetic disorders, and the child's elder sibling was healthy.

Mother had regular antenatal visits and antenatal period was normal. Child was delivered at term with a birth weight of 2.5 kg, by normal vaginal delivery. Child was breast fed soon after birth and postnatal period was uneventful and hence discharged on PND5. Within the first month of life, the mother noted excess cry during handling, limited limb movements, and progressive skin darkening over joints. By 3 months, the infant developed multiple hyperpigmented, lesions over the knuckles, knees, and ankles, and clawing of hands due to contractures. child was feeding well at breast but had poor weight gain.

Physical examination revealed; apathetic child. The skin was thickened with multiple hyperpigmented papulonodular

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lesions, particularly over bony prominences. **(Figure 1)** There was no history of recurrent loose stools. There was clawing of fingers and toes. Abdominal was distented with mild hepatosplenomegaly. Child had underweight and stunting.

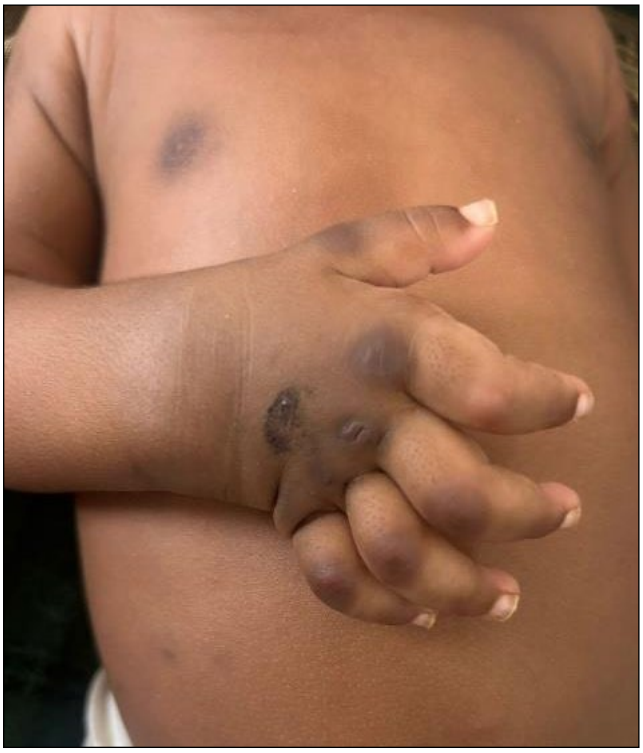

Figure 1: Image shows characteristic hyperpigmentation over knuckles, with extension of metacarpo phalangeal joints and flexion of inter phalangeal joints due to skin thickening. There is significant thickening of skin over bony prominences

Laboratory findings included normal hemoglobin level slightly low serum albumin, normal ESR, normal Ca/P/ ALP. Abdominal ultrasound showed no major abnormalities, and skeletal X-rays revealed osteopenia and periosteal reaction. **(Figure 2)**

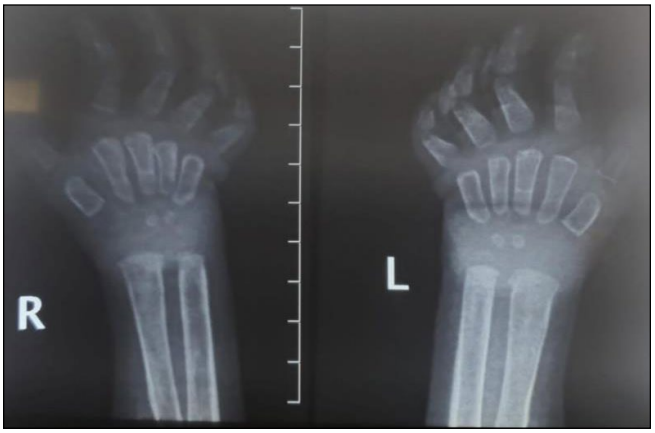

Figure 2: Xray shows osteopenia with joint contractures

A skin biopsy from an ankle lesion demonstrated amorphous, Periodic Acid Schiff (PAS)-positive hyaline deposits in the dermis. **(Figure 3)** Molecular DNA sequencing identified deletion in exon 1 of the *ANTXR2* gene establishing the genetic basis of the disease.

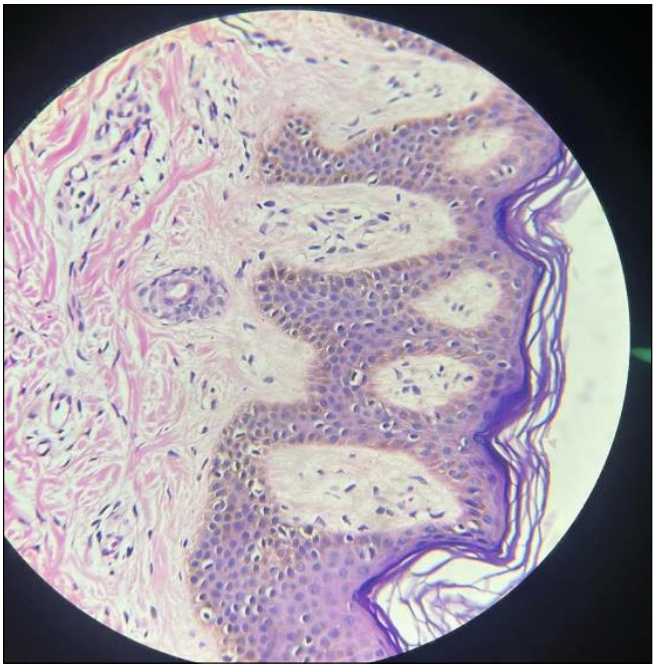

Figure 3: Skin biopsy showing mild atrophy of epidermis. Eosinophilic hyaline material is seen filling papillary dermis causing flattening of suprapappillary dermis. Special stains PAS was positive, alcian blue negative and congo red negative

3. Management and Outcome

Management was supportive, focusing on symptom relief. Physiotherapy was initiated to address joint contractures, but progress was limited due to severe pain. Child succumbed to sudden death while at home at 6 months of age. Prenatal genetic counselling advised for parents for next pregnancy.

4. Discussion

ISH is characterized by diffuse hyaline deposition in multiple tissues, the skin, intestine, muscles, and endocrine glands, leading to a constellation of debilitating symptoms.[7] The *ANTXR2* gene, located on chromosome 4q21.21, encodes a transmembrane protein critical for extracellular matrix assembly. Mutations disrupt thisprocess, causing hyaline accumulation.The clinical presentation in this child aligns with previous reports, which describe joint contractures, skin nodules, as hallmark features.[8] Some reports have described intrauterine growth retardation and decreased fetal movements in children with ISH.

Children with ISH presents in Infancy itself, with a predominant symptoms of pain while handling and decreased spontaneous movements. Skin shows skin thickening and hyperpigmentation with some pearly papules seen predominantly on face, scalp and neck. A perianal examination often shows fleshy nodules in perianal region. There is increased risk of bone fractures due to generalised osteopenia. These children are intellectually normal.

Recurrent infections, are a major cause of mortality, often due to restricted chest wall movement.[9] This condition has a progressive course and children rarely survive beyond second birthday. Mortality occurs from pneumonia or severe diarrhea.

Histopathologically, PAS-positive hyaline deposits are diagnostic, as confirmed in our patient. The overlap between ISH and JHF has led to the proposed term "hyaline fibromatosis syndrome," with ISH representing the severe end of the spectrum. The absence of effective treatments remains a significant challenge. D-penicillamine has shown limited success in improving joint mobility by inhibiting collagen maturation, but its efficacy is inconsistent.[10] Surgical interventions for nodules are often futile due to recurrence.

Genetic counseling is critical, particularly in populations with high consanguinity, to inform families of recurrence risks. Our case underscores the need for early genetic testing to confirm the diagnosis and prognosticate despite the lack of curative therapies. There is a scope for future research on elucidating the mechanisms of immune dysfunction and exploring targeted therapies to mitigate hyaline deposition.

5. Conclusion

This case of ISH, confirmed by a novel *ANTXR2* mutation, illustrates the devastating clinical course of this rare disorder. The patient's presentation with severe joint contractures, skin lesions and coupled with histopathological and genetic findings, reinforces the diagnostic criteria for ISH. The lack of effective treatments highlights the need for research into novel therapeutic strategies. Early genetic testing is essential for diagnosis and counseling, particularly in high-risk populations. This report contributes to the literature on ISH and highlights the importance of multidisciplinary care in addressing its complex manifestations.

6. Source of Funding

None.

7. Conflict of Interest

None.

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