Case Report

Infantile Systemic Hyalinosis: Presentation of Thick Skin and Joint Contractures in a Child with Intractable Diarrhea

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The authors report a case of infantile systemic hyalinosis [ISH] in a 9-month-old female infant who presented with generalized thickening of the skin with progressive joint contractures. The patient also had intractable diarrhea due to protein-losing enteropathy. Other typical findings included gum hypertrophy, hyperpigmentation of the skin above the proximal inter-phalangeal (PIP) joints, and cutaneous nodules on the perianal area. Skin biopsy manifested the deposition of amorphous hyaline material in the dermal layer, confirming the pathogenesis of ISH.

Keywords: Thick skin, Joint contractures, Intractable diarrhea, Perianal nodules, Gum hypertrophy, ANTXR2, Gene

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Infantile systemic hyalinosis [ISH] is a rare autosomal recessive disease characterized by generalized thickened skin due to the deposition of amorphous hyaline material in the dermis[1-3]. The patient characteristically presents with cutaneous findings of hyperpigmentation of the area overlying bony prominences especially above the proximal inter-phalangeal [PIP] joints. Other cutaneous findings are the presentation of pearly papules or nodules on the face, neck, scalp, and especially on the perianal area. The patient usually has progressive joint contractures, osteopenia, and a short stature. Most cases are prone to chronic diarrhea due to protein-losing enteropathy[4], which is the main factor leading to severe malnutrition which exacerbates the chances of infection and sepsis. Mortality usually ensues by 2 years of age in the majority of cases. Diagnosis of this condition can be made by typical clinical findings as well as supporting evidence such as deposition of amorphous hyaline material in the dermal layer of the skin. Due to the rarity of this disease, a diagnosis of ISH can be challenging and most physicians tend to misdiagnose and mistreat. With this report, we propose the use of distinctive clinical findings supported by the histology of skin biopsy to enhance the recognition of this rare disease.

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Case Report

The patient was the second child (G2P1011). The first child was spontaneously aborted at gestational age 4 weeks. The family history was negative for the similar clinical findings to ISH, which included musculoskeletal disease, gastro-intestinal disease, and apparent abnormal cutaneous findings. Consanguinity was noted in the family. In Figure 1, the patient's family line with the positive consanguinity is presented.

The patient was an otherwise healthy, full-term, breech delivery. Even though poor fetal movement was noted, no abnormal findings were found at birth. Her birth weight was 3,100 g. She was regularly breastfed with normal growth and proper weight gain during the first month of life. At the age of 2 months, the patient started to have limited joint movement which began with finger contractures and bilateral hand contractures, as well as limited extension of the hips, knees, and ankles. Plain skeletal radiographs were performed, revealing mild osteopenia with widening of the inter-pedicular distance at the lumbar spine, L1 level.

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An electrodiagnostic study was performed which showed no evidence of polyneuropathy or motor neuropathy. A genetic evaluation was performed, revealing a normal blood chromosome analysis (46, XX). She also tested negative for the SMN1 gene; thereby ruling out spinal muscular dystrophy [SMA]. The patients was followed up by a rheumatologist and diagnosed with juvenile idiopathic arthritis [JIA].

Systemic corticosteroids and non-steroidal anti-inflammatory drugs [NSAIDs] were prescribed for about 1 month: No clinical improvement was observed. At 5 months of age, the patient started to manifest generalized thickening of the skin, hyperpigmented plaque overlying the PIP joints of both hands (Figure 2A) and abnormal painless coalescent perianal hyperpigmented nodules (Figure 2B).

Clinically significant joint contractures persisted and grew more severe. Her hips were held in a frog-leg position (Figure 2C) and could not be fully extended during examination. Within a month (when she was 6 months old), chronic diarrhea was documented and the patient developed severe malnutrition. During this time, she was frequently admitted due to an apparent respiratory tract infection as well as needing parenteral nutritional supplement to improve her overall nutritional status.

Laboratory results revealed persistent low levels of serum protein (3.8 g/dL), albumin (1.5 g/dL), globulin (1.3 g/dL) as well as thrombocytosis (932,000/uL). The patient had low levels of creatinine (0.1 mg/dL) and a mildly elevated aspartate aminotransferase [AST] level (48 to 52 U/L) throughout her hospital stay. She also had a persistent positive stool occult blood as well as stool fat based on microscopy findings. Other laboratory examinations-including complete blood count (with differentials), serum electrolytes, and other renal and liver functions-were within normal range.

Based on multiple apparent clinical findings, the previous diagnosis of JIA was unlikely. The patient was re-assessed by a multi-disciplinary team to identify the correct diagnosis. After sorting through the clinical findings of marked thickening of the skin, multiple progressive joint contractures, perianal nodules and chronic intractable diarrhea, a diagnosis of ISH was proposed.

In fact, a skin biopsy confirming the diagnosis was performed as soon as ISH was suspected. The piece of skin was taken-using a 3-mm punch biopsy-from the most thickened skin at the right dorsal aspect of the patient's wrist. The result of the skin biopsy revealed amorphous eosinophilic hyaline material in the papillary dermis as well as in the subcutaneous layer. Figure 3A shows a homogeneous, pale, hyalinized dermis and cellular proliferation composed of spindle and round cells. Homogenization of the papillary and reticular dermis, filled by amorphous substance, was observed. The hyaline material was positive with periodic acid + Schiff stain (Figure 3B). Taken together, these findings indicated the deposition of hyaline material in the dermal layers, which was the main pathogenesis explaining the clinical findings of ISH.

After the diagnosis of ISH, the patient was

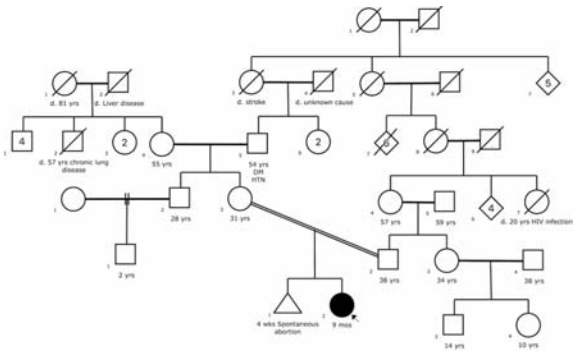

Figure 1. The patient's pedigree revealing positive consanguinity.

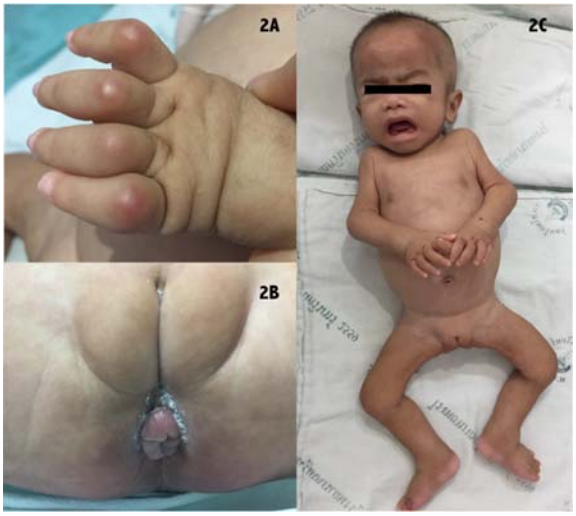

Figure 2. Representing clinical picture of ISH; hyperpigmented plaque overlying PIP joints of both hands (2A), abnormal painless coalescent perianal hyperpigmented nodules (2B), and clinical of joint contractures in a frog-leg position (2C).

frequently admitted due to chronic diarrhea and severe malnutrition. At 11 months of age, she died due to severe sepsis.

Discussion

The authors reported a case with ISH determined by clinical presentation, cutaneous manifestations, and skin histopathology. A complete evaluation of internal organ involvements and molecular gene assessment were not done due to financial limitations.

ISH is a rare inherited condition arising from hyaline material deposition in the tissues[5]. It was first reported by Glover et al[2] in 1991. At that time, the authors proposed that the clinical findings of ISH were similar to another syndrome called Juvenile Hyaline Fibromatosis [JHF][6-8]. Albeit JHF has very similar clinical findings, the clinical onset and severity differ. Since 2009, after the report of gene mutation in the anthrax toxin receptor-2 gene [ANTXR2] on chromosome 4q21 in both ISH and JHF[9], these two diseases are now grouped into Hyaline Fibromatosis Syndrome [HFS][8]. JHF has the same entity of diseases but the severities differ.

ISH is a severe form of HFS representing the more serious clinical course[10] as consequence of the wide-spread deposition of hyaline material throughout the skin, gastrointestinal tract, endocrine glands, and muscles. Onset occurs very early; usually during the first year of life, and affected persons die by the age of 2 years[11-13]. By contrast, JHF has a late onset of manifestation and also presents with less severity.

ISH is an autosomal recessive hereditary disease. Hence, most of the published literature shows positive consanguinity in the family, including in twins[14]. Our patient's pedigree (Figure 1) also showed positive consanguinity in the family; however, the patient was the first person in her family to be diagnosed with this syndrome. According to the autosomal recessive hereditary pattern, each sibling of an affected individual has a 25% chance of being affected. Therefore, genetic counseling is necessary especially with those who present with the less severe form.

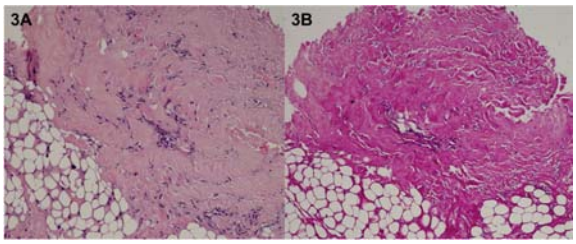

Figure 3. Homogeneous, pale, hyalinized dermis and cellular proliferation comprising spindle and round cells (3A, H&E; original magnification 40X). The hyaline material was positive with periodic acid + Schiff stain. (3B, PAS; original magnification 40X).

The pathogenesis of ISH is unknown; however, it is associated with deposition of hyaline material in many structures (i.e., dermal layers of the skin, liver, spleen, adrenal glands, and musculoskeletal structures). As a consequence of the widespread and massive deposition of hyaline material in many structures, the clinical manifestations are the result of the functional limitations of involved organs. One of the major structures is the musculoskeletal system, which presents as multiple painful joint contractures. Most of the cases usually present with stiffness of the joints resulting in immobility. This manifestation can be easily misdiagnosed with other musculoskeletal and neurological diseases such as JIA, as in our case. Our patient underwent many treatments aimed at treating the clinical course of JIA; by using systemic corticosteroids as well as NSAIDs. Notwithstanding these treatments, no clinically meaningful improvements were observed.

Cutaneous deposition of hyaline material is another major part of this disease. Massive deposition of hyaline in the dermal layer is the cause of generalized thickening of the skin. This manifestation can easily be mistaken for other causes of edematous skin (i.e., other liver or kidney diseases). Other ISH patients have been documented as having chronic diarrhea[4]; this is due to the deposition of hyaline material along the gastrointestinal tract which in turn directly blocks intestinal absorption. Owing to the lack of absorption, patients can also present with protein-losing enteropathy[4], which results in serum albumin depletion, which in turn causes observable edematous skin. Due to the nonspecific clinical findings during the early course of this syndrome in conjunction with its rareness, a correct diagnosis is challenging. Nevertheless, there are differentiating clinical clues that help to make a correct diagnosis. We summarized the distinctive clinical findings that can be found in ISH (Table 1).

Treatment for ISH is currently only symptomatic and supportive[15]: the main goal is nutritional supplementation. Albumin infusion is needed when the patients have severe hypo-

Table 1. Summary of distinctive clinical features of ISH

Skin
Generalized thickening and edematous skin
Skin papules and nodules; any sites (usually on scalp, face, neck)
Hyperpigmentation over bony prominences (usually on PIP and MCP joints, medial and lateral malleoli of the ankles)
Perianal nodules
Gum hypertrophy
Musculoskeletal system
Progressive painful joint contractures
Frog-leg position
Immobility child
Generalized osteopenia from plain radiographs
Gastrointestinal system
Chronic intractable diarrhea
Protein-losing enteropathy
Failure to thrive

ISH = Infantile systemic hyalinosis; PIP = proximal inter-phalangeal; MCP = metacarpo-phalangeal

albuminemia. Some patients may need a gastrostomy tube for feeding. The long-term prognosis of ISH is poor and most patients die by the age of 2 years.

Conclusion

We reported a case of the rare ISH in a 9-month-old female infant who manifested the typical findings of progressive joint contractures, thickening skin, hyperpigmentation over PIP joints, perianal nodules, and intractable diarrhea. Even though this is a rare, complicated disease, which is difficult to make a correct early stage diagnosis, a multi-disciplinary approach helps to recognize the distinctive features and to make a correct diagnosis.

What is already known on this topic?

Infantile systemic hyalinosis [ISH] is a rare inherited disorder with a severe clinical course.

What this study adds?

Due to the rareness of ISH and the variety of non-specific clinical manifestations, diagnosis of the disease is often delayed.

A multi-disciplinary approach and the recognition of the disease's distinctive findings are the keys to a proper investigation and correct management.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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