CASE REPORT

Case series of infantile systemic hyalinosis: suggested diagnostic criterion

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ABSTRACT

Background: Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disease that happens within the first weeks of life. It is present in Saudi Arabia due to positive parental consanguinity. A suggestive diagnostic criterion was proposed which would be helpful in determining ISH.

Case Presentation: Seven children were diagnosed with ISH based on clinical pictures and histopathological examination. A prospective consecutive and observational study was designed to determine the diagnostic criteria of ISH. On clinical examination, all patients had joint contractures which led to frog-like position, hyperpigmentation overlying the distal joints, in addition to failure to thrive. Only five patients of seven (71.42%) had erythematous papules coalesce to form plaque on the posterior neck. Out of seven, four patients (57.14%) had nodules (perianal and subcutaneous), and gingival hypertrophy. Three patients of seven (42.85%) had intractable diarrhea. Just one patient (14.28%) had small pearly skin papules on the face. Hyaline deposits were evident in histopathological examination of the skin biopsies for all the patients. Although, the severity index and genetic study were unavailable

Conclusion: ISH is a congenital disease characterized by excessive hyaline deposits. Diagnostic criterion was evaluated for the seven patients as three major criteria and five minor criteria. It was suggested that the presence of all three major criteria or two major and two minor criteria is essential for the diagnosis of ISH. The diagnostic criterion would help in the early evaluation of the disease prognosis and would enhance early intervention.

Keywords: Infantile systemic hyalinosis, autosomal recessive, joint contracture, perianal nodule.

Introduction

Infantile systemic hyalinosis (ISH) is a rare autosomal recessive progressive disorder characterized by diffuse hyaline deposits in the bone, visceral organs, and skin. The hyaline deposits are evident in histopathological examination of the skin and affected organs. Although the pathogenesis is not understood, the fibroblasts show abnormal cellular interactions with the intracellular matrix. This pathological change is due to capillary morphogenesis-2 (CMG2) gene mutation characterized by lacking the post-translation modification due to the retention of protein-2 in the endoplasmic reticulum [1].

Clinical onset typically occurs within the first few weeks of life. The disease manifestations include joint contractures, osteopenia, short stature, gingival hypertrophy, failure to thrive, frequent infections, malnutrition, abdominal distension, diarrhea, and dermatological manifestations [2].

The diagnosis of ISH is clinically confirmed by the characterized histopathology of the skin biopsy. The main diagnostic clinical manifestations depend on a triad found in most patients including hyperpigmentation over the distal joints, joint contracture, and failure to thrive. The light microscopic examination of the skin biopsy sampled from the erythematous papules or the hyperpigmentation macules shows amorphous eosinophilic hyaline material deposit in the peri-and-vascular wall of the dermis and in the papillary and deep dermis. Other dermatological manifestations are supportive of ISH diagnosis and frequently are seen among patients. Erythematous papules coalesce into plaques on the pre and post-auricular region and neck. Subcutaneous
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nodules are present, especially on the ear lobes. Additional manifestations are present such as small pearly skin papules, gingival hypertrophy, and disfiguring facial features (saddle nose - sunken eyes). Patients have perianal nodules and are unable to speak, sit, or roll over.

Two early clinical signs of ISH are noticeable. The first sign is joint contractures; which are encountered in the first few weeks of life. The joints become painful and tender on the touch. The baby is always crying upon minimal touching of the joints. The second sign is hyperpigmentation over the distal joints (phalangeal, metacarpophalangeal, and malleoli). Other signs might appear gradually during the first 6 months of life.

In this study, the clinical manifestations of the ISH were sought to focus and its value in the diagnosis of this very rare disease. A case series of seven patients of ISH was described who came to the dermatology clinic of the current study tertiary hospital. A prospective consecutive and observational study was designed to determine the diagnostic criteria of ISH.

Cases Descriptions

Case 1

A male patient (22 months old) was a full term of normal pregnancy, with second-degree consanguinity of apparently healthy parents. The patient was referred to the hospital with a history of crying for any touch and joint contractures since the birth. On clinical examination, the patient had a frog-like position secondary to the joint contracture, gingival hypertrophy, saddle nose, and sunken eyes (Figure 1).

The patient had developmental milestones such as being unable to roll over, to speak, and to sit down. He had also abdominal distention, malnutrition, and hyperpigmentation over the distal joints (metacarpophalangeal, phalange, and malleoli) and also on big joints that as elbows and knees. There was coalescing of erythematous papules forming thick plaque on the posterior neck and peri-auricular region and nodules on both earlobes (Figure 2).

There were fleshy nodules in the perianal region. There was a family history of a bilateral extra finger in the grandmother and overlapping the fifth finger on the fourth in the uncle (mother’s side). The ISH was suspected, and the light microscopic examination of the skin biopsy demonstrated the deposition of amorphous Alcian blue stain-positive material around the blood vessels and in the papillary and deep dermis (Figure 3).

Case 2

A 20-month-old female, the second child of non-consanguinity parents, was presented. The patient was referred to the clinic with arthrogryposis, this diagnosis was already made by her pediatrician when she was 6 months old. Despite the intense physiotherapy, the painful joint contractures were progressing. On clinical examination, the patient had joint contractures leading to frog like position and dermatologic features (Figure 4).

There was no family history of a similar disease. The ISH was suspected and the histopathology examination of the skin biopsy confirmed the diagnosis.

Case 3

A 7-month-old male was the fourth child (two sisters and one brother) of first-degree consanguinity parents. The patient was admitted to the pediatric hospital

Figure 1. The gingival hypertrophy and saddle nose.
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Case 4

A 4-month-old female, the sister of the first patient, was presented. The case was presented to the dermatology clinic with hyperpigmentation over the joints and a history of crying to the light touch of these joints. On clinical examination, the patient had a frog-like position secondary to joint contractures and the patient was unable to rollover. Hyperpigmentation was over the metacarpophalangeal, malleoli, and elbow joints. The histopathology of the skin biopsy of hyperpigmentation macule showed superficial and deep dermal depositions of positive Periodic acid-Schiff stain (PAS) and diastase-resistant homogenous hyaline material with onion skin arrangement around the capillary.

Case 5

A premature 11-month-old female was presented. She was the second child of first-degree consanguinity of apparently healthy parents and brother. Her birth weight was 1.5 kg and she was admitted to the intensive care unit after the delivery for 1 month. The patient presented to the emergency room of a pediatric hospital with intractable diarrhea for more than 3 months, weight loss, and fever. After admission, dermatologic consultation was requested to evaluate seborrheic dermatitis-like plaque on the posterior of the neck and the hyperpigmentation over the distal joints. The patient had a frog-like position, crying for a light touch of the joints, unable to site, and unable to rollover. According to the clinical manifestations and the histopathology of the skin and rectosegmental biopsy, the diagnosis of ISH was made. The patient died 1 month later secondary to pneumonia.

Case 6

A 4-month-old male, a brother of patient 3, was presented to a dermatologic clinic with hyperpigmentation over joints, a history of crying in response to the light touch of the joints, and failure to thrive. The joints were contractured with hyperpigmentation over the metacarpophalangeal, phalange, and malleoli joints. The patient had mild erythematous plaque similar to seborrheic dermatitis on the posterior of the neck and one café au lait maculae on the dorsum of the left hand. There were neither nodules nor papules in the subcutaneous and on the posterior neck.

Case 7

A 5-month-old female, the first child of first-degree consanguinity of apparently healthy divorced parents. A family history of the disease from the father’s side was not obtained while it was negative on the mother’s side. The patient presented to the hospital with a chronic history of intractable diarrhea not respond to treatment. On clinical examination, painful joint contractures were present which led to the patient crying for any touch, being unable to rollover, mild hyperpigmentations on the interphalangeal joints of the fingers and toes and malleoli, failure to thrive, and mild gingival hypertrophy. There was no hyperpigmentation on the metacarpophalangeal, and elbow, no perianal nodule, and no subcutaneous nodule. The histopathology of the hyperpigmented macule of the skin biopsy showed perivascular deposition of pale eosinophilic hyalinized collagen-like material in the dermis and subcutaneous layer with weak positive PAS stain. The sigmoid biopsy showed unremarkable changes (Table 1).
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Discussion

ISH is a rare fatal autosomal recessive disorder. It was first described in 1978 by Nézelof et al. [1] in a Portuguese boy who presented with painful limited joint mobility, areas of hyperpigmented skin, and gum hyperplasia at the age of 1 month. In 1986, Landing and Nadora [2] reported four infants with similar clinical features of thickened skin, focal nodular lesions, hypertrophy of gingival mucosa, and painful joint contractures. These infants also had recurrent infections, diarrhea, and growth failure and none of them survived beyond 20 months of life. The clinical appearance was found to be similar to juvenile hyaline fibromatosis, a disorder of collagen metabolism, which presents in older children but does not show rapid progression and is not fatal [2]. Further cases were reported, and in the majority, the manifestations began in the early weeks of life. Death frequently occurred within 2 years of life secondary to infection and diarrhea. The cutaneous lesions have been described as tiny pearly papules on the face, erythematous plaques on the neck, and subcutaneous and perianal nodules. The disease is characterized by intense pain and immobility in the joints during the initial phase followed by joint contractures with frog leg posturing of the limbs. The hands show arthrogryposis with hyperpigmented plaques on the metacarpal and proximal interphalangeal joints [3]. Other clinical features seen in ISH include rigidity of the spine, hyperpigmentation over bony prominence, and saddle nose deformity [4].

The histological examination of the skin and other organ biopsies such as the heart, trachea, spleen, esophagus, stomach, small and large intestines, adrenal glands, skeletal muscle, thyroid, and lymph node demonstrate deposits of amorphous hyaline material. The deposition in the skin is seen in both the dermis and vessel wall with thickening of collagen and irregular hyperplasia of the epidermis [3]. The ultra-structural feature of the hyaline material deposits resembles type VI collagen [5].

ISH is caused by a mutation in the anthrax toxin receptor 2 gene (ANTHRAX2). The genetic studies have mapped the responsible gene to chromosome 4q21. It encodes CMG 2 which is a transmembrane protein with strong binding to laminin and collagen type 46. The abnormal interaction of CMG 2 and laminin results in dysregulation of cell-cell and cell-matrix interaction, which could lead to extracellular deposits of hyaline material [6-9].

The differential diagnosis of ISH includes juvenile hyaline fibromatosis, mucopolysaccharidoses, Farber syndrome, lipoid proteinosis, and Winchester syndrome have been established (Table 2).

There is no effective treatment for ISH. Physiotherapy and medications including penicillamine, methotrexate, and NSAIDs have been tried with variable success for painful joint contractures [10]. Gene studies need to be carried out to understand and develop a treatment for this otherwise fatal disorder.

At present 54 cases have been reported in the literature, out of which 23 cases are from the Middle East [10]. This study reported seven cases of ISH seen in the Dermatology clinic of King Fahad Medical City, Riyadh, over the past 2 years. Six patients were born of consanguineous marriage and two patients were siblings. All these cases presented with the classical clinical features which included gingival hyperplasia, erythematous plaques and nodules, hyperpigmentation over the joints, and painful joint contracture. Hyperpigmentation over the contracture joints was the earliest sign to appear even directly after delivery or within a few weeks, followed by erythematous papules and plaques at the age of 3-4 months. All patients showed failure to thrive, five had abdominal distension, three had chronic diarrhea and one had pneumonia. Two patients with chronic diarrhea underwent sigmoidoscopy and a mucosal biopsy from two patients who had chronic diarrhea failed to show...
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The collective clinical criteria of ISH showed consistency of tender joint contracture with hyperpigmentation over the distal joints, failure to thrive, and presence of hyaline deposit in the dermis. These criteria were considered the major diagnostic criteria of ISH. The other criteria of subcutaneous nodules on ear lobes, perianal nodules, erythematous plaques on the neck, gingival hypertrophy, and intractable diarrhea as minor criteria.

On follow up, one infant died due to chronic diarrhea and recurrent infections at the age of 9 months and another at the age of 11 months due to pneumonia. There was no cardiac involvement in any of the presented patients. Skin biopsies were done and demonstrated amorphous eosinophilic hyaline deposits in the dermis consistent with the diagnosis of ISH.

The diagnosis for all the patients was delayed as physicians ignored the dermatological manifestation. To prevent delay in the diagnosis, a criterion based on the clinical features seen in the presented patients and a review of other case reports was suggested (Table 3).

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**Table 1. Summary of the clinical signs of ISH in the seven patients.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone abnormalities (joint contractures- short stature-osteopenia)</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hyperpigmented macules over the distal joints</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gingival hypertrophy</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>_</td>
<td>2</td>
<td>1</td>
<td>_</td>
</tr>
<tr>
<td>Erythematous papules on the posterior neck</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>_</td>
<td>1</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Perianal nodules</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>_</td>
<td>1</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Small pearly skin on the face</td>
<td>1</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Deposition of hyaline in the dermis</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>_</td>
<td>1</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>_</td>
<td>1</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Consanguinity between parents</td>
<td>Second</td>
<td>degree</td>
<td>_</td>
<td>1</td>
<td>Second</td>
<td>degree</td>
<td>3</td>
</tr>
</tbody>
</table>

Clinical features evident at birth or within the first 3 months | 7 | 6 | 5 | 4 | 3 | 2 | 1 |

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**Table 2. Differential diagnosis of ISH.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile hyaline fibromatosis</td>
<td>Papulonodular skin lesions, gingival hyperplasia, joint contractures, and osteolytic bone lesions; prolonged survival</td>
</tr>
<tr>
<td>Winchester syndrome</td>
<td>Thickening, hyperpigmentation, and hypertrichosis of skin; gum and lip hypertrophy; corneal opacities; musculoskeletal abnormalities</td>
</tr>
<tr>
<td>Farber syndrome</td>
<td>Erythematous papules and subcutaneous nodules over joints, tendons, and pressure points; hoarseness; joint deformities; internal organs affected</td>
</tr>
<tr>
<td>Lipoid proteinosis</td>
<td>Yellowish-white papules and nodules on skin and mucosae; &quot;string of pearls&quot; appearance on upper eyelids; varioliform scarring; hypotrichosis; hoarseness; thickened lips; nodules or grooves on tongue; internal organs may be affected</td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
<td>MPS I (Hurler): hypopigmentation and thickening of the skin; hypertrichosis; dental abnormalities; thick lips and protuberant tongue MPS II (Hunter): white papules and nodules on back, arms, and thighs</td>
</tr>
</tbody>
</table>

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**Table 3. Proposed diagnostic criterion based on the clinical features seen in the presented patients and review of other case reports.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major criterion</td>
<td>Painful joint contracture with hyperpigmentation over the distal joints Failure to thrive Presence of hyaline deposit in the dermis</td>
</tr>
<tr>
<td>Minor criterion</td>
<td>Subcutaneous nodules on ear lobes Perianal nodules Erythematous plaques on neck Gingival hypertrophy Intractable diarrhea</td>
</tr>
</tbody>
</table>

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any deposits of hyaline. Whereas the skin biopsy of the same patients showed hyaline deposition in the dermis.
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It was suggested that the presence of all three major criteria or two major and two minor criteria are essential for the diagnosis of ISH.

**Conclusion**

ISH is a congenital disease characterized by excessive hyaline deposits. Diagnostic criteria were evaluated for the seven patients as three major criteria and five minor criteria. It was suggested that the presence of all three major criteria or two major and two minor criteria is essential for the diagnosis of ISH. The diagnostic criteria would help in the early evaluation of the disease prognosis and would enhance early intervention.

**Conflict of interest**

The author declared that there is no conflict of interest regarding the publication of this case report.

**Funding**

None.

**Consent for publication**

Informed consent was obtained from the participant.

**Ethical approval**

Ethical approval is not required at our institution for an anonymous case report.

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**References**


