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Case Report

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INFANTILE SYSTEM HYLONOSIS CASE REPORT AND SURGICAL MANAGEMENT

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ABSTRACT

Infantile systemic hyalinosis (ISH) is a rare, progressive and fatal autosomal recessive disease, characterized by diffuse hyaline deposits in the skin, gastrointestinal tract, muscle and endocrine glands.[1] The clinical features are evident either at birth or within the first 6 months of life. This disease is usually fatal within 2 years of life. It is manifested by painful progressive joint contractures, thickened skin with hyperpigmentation over the bony prominences, susceptibility to bone fractures, infections and gingival hyperplasia. Here we report a case of a 5-year-old boy with a physical disability since birth, painful joints contractures, growth retardation, thickened skin with hyperpigmentation, and gingival hyperplasia.[2] Histopathologic and molecular studies confirmed the diagnosis of ISH in this patient. We describe the surgical management for this patient and the treatment outcomes. Since no treatment is currently available for this condition, symptomatic management and pain control are the only ways to manage such cases.

KEYWORDS: Infantile systemic hyalinosis (ISH), Progressive joint contractures, gingival hyperplasia.

INTRODUCTION

Infantile Systemic Hyalinosis (ISH; MIM #236490) is a rare autosomal recessive disorder of unknown pathogenesis. Clinical onset is during the first six months of life, manifested by pain when handled, painful joint contractures leading the infant to assume the frog leg position, significant immobility in the affected infant, a protein-losing enteropathy, and an increased susceptibility to bone fractures and infections. Dermatologic manifestations include thickened skin with livid-red hyperpigmentation overlying bony prominences, small pearly papules predominantly on the head (face, ears, neck), and fleshy perianal nodules. Oral disorders include nodular lip enlargement and gingival hypertrophy, which may be severe enough to interfere with feeding, and may result in poor oral hygiene and dental caries. The disorder is progressive, and the course is often fatal in the first years of life, mostly due to recurrent chest infections or diarrhea (Stucki et al., 2001, Lindvall et al., 2008, Nofal et al., 2009, Criado et al., 2004).[8,9,11]

We hereby describe the case of a 5-year-old boy with ISH, presenting at the age of 5 years with physical disability, painful joint contractures, gingival hyperplasia and hyperpigmentation. We also illustrate the surgical management for this patient and the treatment outcomes.

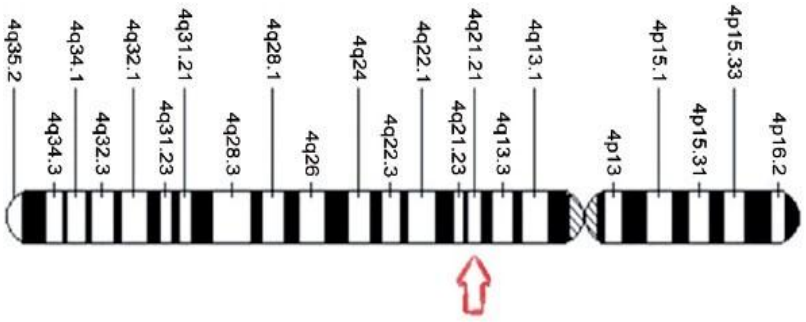
CASE REPORT

A 5-year-old boy presented to the Oral and Maxillofacial Surgery clinic for the treatment of his gingival hyperplasia. The patient was the first child of a consanguineous marriage from Saudi Arabian parents (first-degree cousins). Family history was negative for similar clinical findings, and the patient has a healthy younger brother. The patient was the product of a normal full-term pregnancy and delivery. At birth, the delivering doctor noticed a skeletal anomaly in the infant's left foot, and informed the mother that her child has a physical disability.

During the infant's first days of life, his mother noted that he cried every time he was handled, and he also had persistent diarrhea. Doctors were unable to reach a diagnosis at this point, and analgesics were prescribed for pain management. Physical therapy was initiated to improve the mobility of the upper and lower limbs. With time, the joint contracture worsened and spread to involve the whole body, and by this time, physical therapy was ineffective in delaying the progress of the disease.

At 11 months of age the mother started to notice mucosal changes in the form of gingival hyperplasia. His skin appeared thicker with hyperpigmentation over the bony prominences, and he also developed perianal nodules. Disfiguring changes of the face such as prominence of the forehead, a widened nasal bridge and sunken eyes

started to progress by the completion of the first year (Figure 1). At the age of 2 years and 9 months, three cutaneous biopsies were obtained from the neck, abdomen and forearm. Histopathologic examination demonstrated extensive dermal hyalinosis and elastosis. DNA analysis confirmed a mutation in the ANTXR2 gene located in the chromosome 4q21, which codes for capillary morphogenesis gene 2 (CMG2).



Diagrammatic representation of chromosome 4 showing the locus of CMG2 gene (red arrow)

Genetic counseling was offered to the parents at this point, and they showed interest in Pre-implementation Genetic Diagnosis (PGD). The patient's mental development was normal for his age, with no signs of any delayed cognitive function. He has had multiple visits to the Emergency Department over the past months for the treatment of his recurrent respiratory infections and diarrhea. The gingival hyperplasia progressively increased and had reached a size that was interfering with the patients feeding, speech, and oral hygiene. His referring plastic surgeon has been managing the multiple skin nodules, the excess skin of the right ear, as well as the scalp enlargement. Furthermore, the patient had difficulty breathing, and has been snoring during sleep due to adenoid enlargement, which was being managed by a pediatric ENT surgeon.

On examination upon presentation, the patient demonstrated most of the features of ISH; (Figure 1B, 2) Short stature (what's the height), severe joint contractures with a "frog-leg" position, growth retardation, and pain with movement and while handling. Gingival hyperplasia was noticeable, yet it was difficult to assess clinically because of limitation in mouth opening. Gingival hyperplasia was covering all the teeth and extending beyond the gingival mucosa, displacing the upper and lower lips in an outward direction. Enlarged nodules over the lower lip were present (Figure 2).

Cutaneous examination revealed the presence of multiple, skin-colored pearly papules of variable sizes over the face, bilateral ears, and neck. The patient had moderate skin hyperpigmentation, abnormal and ulcerating scalp enlargement (Figure 2), and perianal nodules. He was admitted for surgical management of his gingival hyperplasia, the left ear excess skin, and the enlarged adenoids. Consultation with pediatric surgery regarding the perianal nodules, and the possible need for gastrostomy feeding tubes post-operatively was done, and no surgical intervention was indicated. After extensive pre-operative work-up, he was taken to the Operating Room to undergo gingivectomy by our team, tracheostomy and adenoidectomy by the ENT team, and right ear skin excess excision by plastic surgery.

Under general anesthesia the ENT team first performed a tracheostomy (Figure 3, 4). Our team took over and gingivectomy was carried out by electrocautery until all the teeth were exposed. The patient had a full primary dentition. Hemostasis was achieved and no intraoral bleeding was observed. Furthermore, de-bulking of the lower lip nodules was done. (Figure 5 A, B)

The patient was then handed over to the ENT team for adenoidectomy, followed by plastic surgery for excision of the left ear skin excess. At the end of the surgical operation, the patient was transferred to the pediatric ICU unit for close monitoring. Shortly thereafter, he was found to be hemodynamically stable and was shifted to a regular ward, with close follow up by all involved teams.

After a couple of days the patient reported right upper dental pain. A pedodontist was consulted, and recommended dental rehabilitation under general anesthesia. The patient underwent restoration of multiple carious teeth, extraction of the lower central incisors, and placement of stainless-steel crowns for the upper molars, all under general anesthesia with the tracheostomy tube.

After the gingivectomy and dental rehabilitation, the patient oral intake improved, and he could chew with his teeth, and consume both soft and hard food, after he had been on a strict liquid diet for the past years. Pronunciation of words improved, and his speech became much clearer. He is under close follow-up to ensure that he is improving, and his mother was given instructions regarding the care and maintenance of the tracheostomy site. A home health care plan was formulated for the patient to start upon discharge from the hospital.

Figures

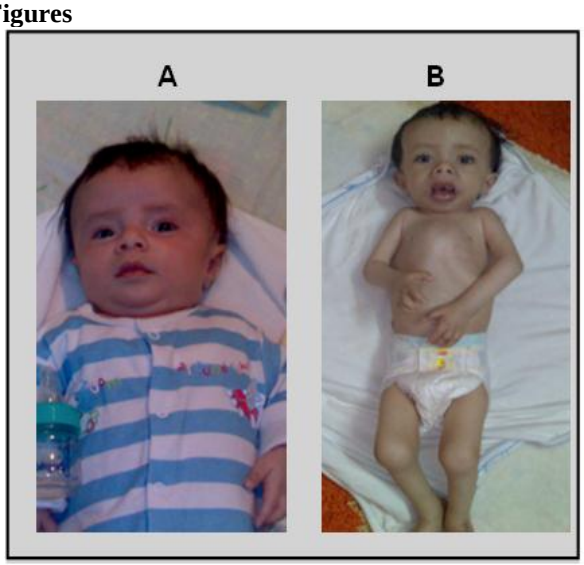


Figure 1: Pictures obtained for the patient showing the progression of the clinical presentation of infantile systemic hyalinosis. A: at the age of 3 months, B: at the age of 2 years.

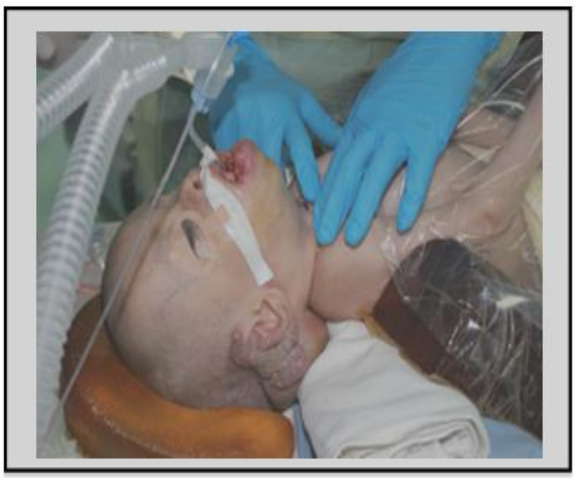


Figure 2: Intra-operative picture of the patient after oral intubation was done. Right ear skin excess is noted here as well.

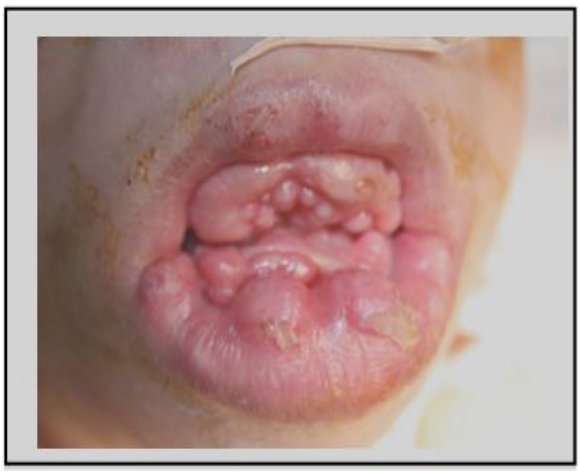


Figure 3: Intra-operative picture of the gingival hyperplasia prior to surgical excision.

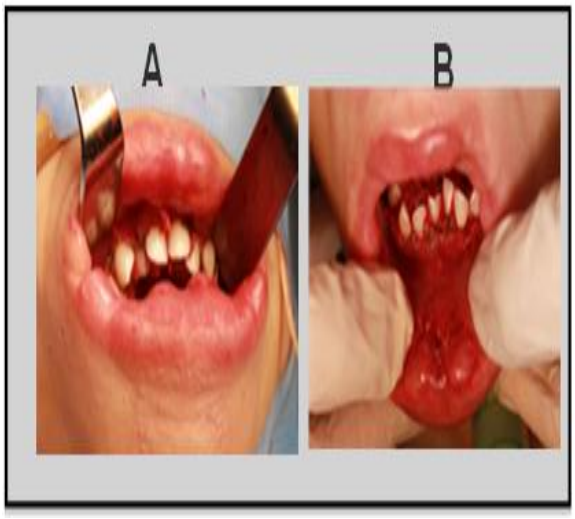


Figure 4: Intra-operative picture after excision of gingival hyperplasia, A: Upper teeth exposed after gingivectomy, B: Lower teeth exposed, also lower lip nodules decreased in size after de-bulking.

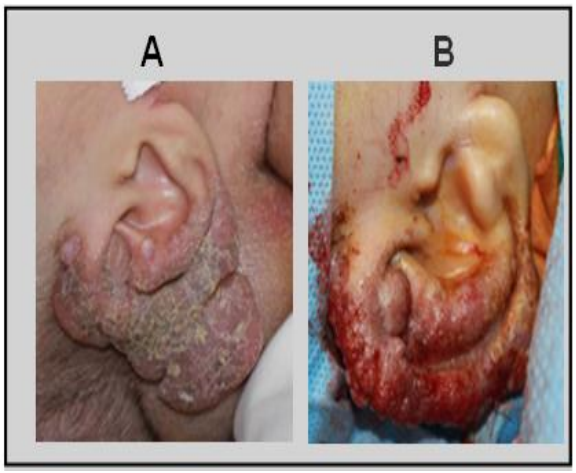


Figure 5: Intra-operative picture of the right ear, A: Before excision of excess skin, B: After excision.

DISCUSSION

Infantile systemic hyalinosis (ISH) is a rare, progressive, and fatal autosomal recessive disease that usually presents at birth or within the first few months of life (Shin et al., 2004).[10] It was initially described by Landing and Nadorra[7] in 1986, when they described the post mortem findings in 4 children with widespread deposits of a hyaline material in different tissues. These children suffered clinically from thickness and focal nodularity of their skin, short stature, gum hypertrophy, fleshy anal nodules, reduced movement, joint contractures, osteoporosis, growth failure, diarrhea, and recurrent infections (Criado et al., 2004, Landing and Nadorra,[4,7] 1986). Most of these clinical features were present in our patient. The patients described in the literature died between the ages of 10 months to three years, mostly secondary to recurrent chest infections and diarrhea. However, improvement in clinical care may

permit prolonged survival of patients with ISH, as in the case of our patient who is in his 5th year of life (Stucki et al., 2001).[11]

Other atypical features of ISH include the reduction of fetal movements, rigidity of the spine, joint swelling, protein losing enteropathy, edema, recurrent vomiting, saddle nose deformity, sunken eyes, and pathologic fractures (Lindvall et al., 2008).[8] Of these features, our patient demonstrated sunken eyes, a widened nasal bridge, and diarrhea. He had age appropriate social and language developmental milestones, although physical growth was retarded. Few authors have debated about the existence of two separate disorders, namely, JHF and ISH. Attempts have been made to differentiate between ISH and JHF. Comparison has been made between our case and the two hyalinosis [Table 1]

Table 1: Table showing the comparison between ISH and JHF and our case

Skin	ISH	JHF	Our case
Papular skin lesions	+	+	+
Thickened skin	+	–	+
Gingival hyperplasia	+	+	
Perianal nodules	+	+	-
Large nodules/tumors	–	+	-
Hyperpigmented plaques	+	–	+
Joints and bones			
Joint contractures	+	+	+
Osteoporosis/osteopenia	+	+	+
Osteolysis	+	+	-
Others			
Persistent diarrhea	+	–	+
Recurrent infections	+	–	-
Visceral involvement	+	–	-
Short stature	+	–	*
Prolonged survival	–	+	*

ISH: Infantile systemic hyalinosis, JHF: Juvenile hyaline fibromatosis

Pathologic examination of the skin and affected viscera demonstrates deposits of amorphous eosinophilic hyaline material, which was observed in the examination of the tissue samples obtained from our patient. The nature of this hyaline material is uncertain; however, some studies have illustrated an ultrastructural fibrillogranular material with a banding pattern identical to type VI collagen, which may be normally present in the dermis (Glover et al., 1992).[6]

While the pathogenesis of this disorder remains unclear, inactivating mutations in the gene encoding capillary morphogenesis gene 2 (CMG2) have been investigated as a cause. CMG2 is a transmembrane protein that binds the extracellular matrix proteins laminin and collagen IV (Bell et al., 2001).[2] CMG2 has been shown to result not only in ISH, but also in juvenile hyaline fibromatosis (JHF), a milder form of the disease with a later onset (Dowling et al., 2003).[5] ISH and JHF patients' derived fibroblasts have been shown to have abnormal CMG2/laminin contact, suggesting that the loss of normal cellular interactions with the extracellular matrix may underlie part of the disease pathophysiology. Genetic DNA analysis in our case confirmed a mutation in the ANTXR2 gene located on chromosome 4q21, which codes for CMG2 protein (Lindvall et al., 2008).[8]

Although ISH was initially thought of as a rare disease, there are increasing numbers of case reports published in the literature. In 2000, only 18 cases of ISH had been reported, however another 34 have been added to the list since then, 19 being from a referral center in Saudi Arabia (Lindvall et al., 2008).[8] Cases of ISH have been reported from all ethnic groups; however, it has been observed that many cases have been of Middle-Eastern origin (Lindvall et al., 2008, Al-Mayouf et al., 2005, Buyukgebiz et al., 2003).[8,1,3] This increased incidence may be due to higher rates of consanguinity among this population, or it may be due to higher carrier frequency as postulated by Al-Mayouf et al (Al-Mayouf et al., 2005).[1] Additional genetic studies will be needed to help in clarifying this hypothesis.

The prognosis of ISH is poor, and most treatments have not proven beneficial. Currently, the only available treatments revolve around symptomatic relief. Gingivectomy with release of contractures and excision of skin nodules are the main symptomatic therapies that can be offered. Despite physical therapy, the joints of patients with ISH become progressively stiffer, requiring chronic pain control (Shin et al., 2004).[10]

Early diagnosis and recognition of the painful joint contractures in infancy will help in pain management, decrease the invasive tests performed, and increase patient comfort. Correct diagnosis of the disease using clinical findings and genetic studies is important for family planning and counseling. Furthermore, thorough structural analysis of the genetic mutations in this disease may provide added insight into the function of the CMG2 protein and the molecular pathophysiology of ISH.

REFERENCES

1. Al-Mayouf, S. M., Almehaidib, A., Bahabri, S., Shabib, S., Sakati, N. & Teebi, A. S. Infantile systemic hyalinosis: a fatal disorder commonly diagnosed among Arabs. *Clin Exp Rheumatol*, 2005; 23: 717-20.
2. Bell, S. E., Mavila, A., Salazar, R., Bayless, K. J., Kanagala, S., Maxwell, S. A. & Davis, G. E. Differential gene expression during capillary morphogenesis in 3D collagen matrices: regulated expression of genes involved in basement membrane matrix assembly, cell cycle progression, cellular differentiation and G-protein signaling. *J Cell Sci.*, 2001; 114: 2755-73.
3. Buyukgebiz, B., Ozturk, Y., Arslan, N. & Ozer, E. A rare cause of protein-losing enteropathy and growth

retardation in infancy: infantile systemic hyalinosis. *Turk J Pediatr*, 2003; 45: 258-60.
4. Criado, g. R., Gonzalez-Meneses, a., Canadas, m., Rafel, e., Yanes, F. & De Terreros, I. G. 2004. Infantile systemic hyalinosis: a clinicopathological study. *Am j med genet a*, 129a: 282-5.
5. Dowling, O., Difeo, A., Ramirez, M. C., Tukel, T., Narla, G., Bonafe, L., Kayserili, H., Yuksel-Apak, M., Paller, A. S., Norton, K., Teebi, A. S., Grum-Tokars, V., Martin, G. S., Davis, G. E., Glucksman, M. J. & Martignetti, J. A. 2003. Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. *am j hum genet*, 73: 957-66.
6. Glover, M. T., Lake, B. D. & Atherton, d. j. clinical, histologic, and ultrastructural findings in two cases of infantile systemic hyalinosis. *pediatr dermatol*, 1992; 9: 255-8.
7. Landing, B. H. & Nadorra, R. infantile systemic hyalinosis: report of four cases of a disease, fatal in infancy, apparently different from juvenile systemic hyalinosis. *pediatr pathol*, 1986; 6: 55-79.
8. Lindvall, L. E., Kormeili, T., Chen, E., Ramirez, M. C., Grum-Tokars, V., Glucksman, M. J., Martignetti, J. A., Zaragoza, M. V. & Dyson, S. W. Infantile systemic hyalinosis: case report and review of the literature. *j am acad dermatol*, 2008; 58: 303-7.
9. Nofal, A., Sanad, M., Assaf, M., Nofal, E., Nassar, A., Almokadem, S., Attwa, e. & Elmosalamy, K. Juvenile hyaline fibromatosis and infantile systemic hyalinosis: a unifying term and a proposed grading system. *j am acad dermatol*, 2009; 61: 695-700.
10. Shin, H. T., Paller, A., Hoganson, G., Willner, J. P., Chang, M. W. & Orlow, S. J. Infantile systemic hyalinosis. *j am acad dermatol*, 2004; 50: s61-4.
11. Stucki, U., Spycher, M. A., Eich, G., Rossi, A., Sacher, P., Steinmann, B. & Superti-furga, a. Infantile systemic hyalinosis in siblings: clinical report, biochemical and ultrastructural findings, and review of the literature. *am j med genet*, 2001; 100: 122-9.
12. Finlay AY, Ferguson SD, Holt PJA. Juvenile hyaline fibromatosis. Br J Dermatol, 1983; 108: 609–16.
13. Lubec B, Steinert I, Breier F, Jurecka W, Pillwein K, Fang-Kircher S. Skin collagen defects in a patient with juvenile hyaline fibromatosis. Arch Dis Child., 1995; 73: 246–8
14. Urbina F, Sazunic I, Murray G. Infantile Systemic Hyalinosis or Juvenile Hyaline Fibromatosis. Pediatr Dermatol, 2004; 21: 154–9.
15. Yesudian P, Janaki VR, Thambiah AS. Juvenile hyaline fibromatosis. Int J Dermatol, 1984; 23: 619–20.
16. Sahn EE, Salinas CF, Sens MA, Key J, Swiger FK, Holbrook KA. Infantile systemic hyalinosis in a black infant. Pediatr Dermatol, 1994; 11: 52–60.
17. Hanks S, Adams S, Douglas J, Arbour L, Atherton DJ, Balci S, et al. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet, 2003; 73: 791–800.
18. Dhingra M, Amladi S, Savant S, Nayak C. Juvenile hyaline fibromatosis and infantile systemic hyalinosis: Divergent expressions of the same genetic defect? Indian J Dermatol Venereol Leprol, 2008; 74: 371–4.