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(CASE REPORT)

Management of Scalp Nodules and Systemic Manifestations in Hyaline Fibromatosis Syndrome

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Abstract

Hyaline fibromatosis syndrome (HFS) is an extremely rare autosomal recessive disorder caused by mutations in the *ANTXR2* gene, leading to the accumulation of hyaline material in various tissues. It encompasses two clinical phenotypes previously thought to be distinct: Juvenile Hyaline Fibromatosis (JHF) and Infantile Systemic Hyalinosis (ISH). We report the case of a 6.5-year-old male, born to consanguineous parents, presenting with a characteristic triad: multiple subcutaneous nodules (primarily on the scalp), pearly skin papules, and severe gingival hyperplasia. The patient also exhibited debilitating joint flexion contractures (resulting in a "frog-leg" posture) and a history of chronic diarrhea and recurrent respiratory infections. Imaging revealed cranial osteolytic lesions, and histopathological analysis confirmed the diagnosis of hyaline fibromatosis. The patient underwent successful surgical excision of the scalp masses followed by skin grafting. This case illustrates the phenotypic overlap between JHF and ISH, supporting the current classification of these entities as a single disease spectrum. While cognitive functions are preserved, physical prognosis depends on the severity of visceral involvement and the management of functional impairments. Early clinical recognition is essential for appropriate multidisciplinary management and genetic counseling. HFS should be considered in the differential diagnosis of pediatric patients presenting with typical cutaneous lesions and joint contractures.

Keywords: Hyaline fibromatosis syndrome; *ANTXR2* gene; Juvenile hyaline fibromatosis; Infantile systemic hyalinosis; Case report

1. Introduction

Hyaline fibromatosis syndromes (HFS) are exceedingly rare autosomal recessive disorders caused by *ANTXR2* gene mutations, leading to extracellular matrix dysfunction. First described in the mid-20th century, their clinical presentation is highly pleomorphic, ranging from localized forms to severe systemic involvement. Diagnosis relies on clinical, histological, and genetic findings, while management remains symptomatic. [1]

The clinical spectrum includes hallmark cutaneous lesions, such as pearly papules (nasolabial folds, neck, perianal area) and large subcutaneous nodules, primarily on the scalp [2, 3] Gingival hyperplasia is frequent and can severely impair nutrition and oral hygiene [4].

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The most debilitating feature is painful joint flexion contractures, leading to a "frog-like" posture in infants and prolonged bedrest in adults [5, 6]. Bone involvement may include osteoporosis and osteolytic lesions [7].

Severe cases often involve systemic infiltration, particularly of the gastrointestinal tract, resulting in protein-losing enteropathy, malabsorption, and failure to thrive [8, 9] Other visceral involvements (heart, thyroid, muscles) are also possible [10]. Histologically, Juvenile Hyaline Fibromatosis (JHF) and Infantile Systemic Hyalinosis (ISH) are indistinguishable, characterized by abundant eosinophilic deposits and spindle-shaped fibroblasts (1). Electron microscopy further reveals characteristic fibrogranular material within vacuoles [11, 12].

Recent genetic studies identified a common mutation on chromosome 4q21 encoding capillary morphogenesis protein 2. Given the overlapping clinical, ultrastructural, and genetic features, it is now widely suggested that JHF and ISH represent different phenotypic expressions of a single disease spectrum rather than distinct entities.

2. Case Report

Patient Presentation and History A 6.5-year-old male, born to second-degree consanguineous parents following an uncomplicated full-term vaginal delivery, presented with three painless scalp swellings that had been slowly enlarging over the past year. Additionally, he exhibited raised lesions on the face and perianal region, which had been increasing in number for three years. At the time of admission, he presented with a 10-day history of fever, cough, and rhinorrhea, with a background of recurrent hospitalizations for bronchopneumonia and diarrhea. His mother reported a loss of limb mobility since age 3, resulting in an inability to stand or walk. Family history was unremarkable for similar conditions.

Physical Examination Clinical examination revealed three mobile, non-tender swellings on the scalp (two bilateral and one occipital), measuring 4 cm × 5 cm, 7 cm × 6 cm, and 3 cm × 2 cm [Figure 1]. Overlying alopecia was noted. These masses were cystic in consistency, exhibiting positive fluctuance and transillumination. One lesion showed hemorrhagic crusting and active bleeding. No underlying bony deformities were palpable, and regional lymphadenopathy was absent.

Facial features included a depressed nasal bridge and multiple asymptomatic, pearly pink papules (1–5 mm) clustered around the nasolabial folds, nose, perioral area, eyebrows, and pinnae [Figure 1]. Similar tiny, shiny, moist pink papules were observed in the perianal region, alongside a 1–5 cm linear, fleshy pink plaque in the intergluteal cleft and lower back. The patient exhibited painful flexion contractures of the elbows and knees, resulting in a characteristic "frog-leg" posture. Dental examination revealed nodular gingival hyperplasia . Other findings included macrocephaly, facial hirsutism, and almond-shaped eyes. Palmar and plantar dermatoglyphics were normal.

Diagnostic Investigations A brain CT scan revealed multiple scalp masses associated with cranial osteolytic lesions, consistent with the underlying systemic disease. A skin biopsy was performed; histopathological analysis confirmed a diagnosis of juvenile hyaline fibromatosis (JHF) with inflammatory changes and no evidence of malignancy. [Figure 2].

Management and Outcome The patient underwent surgical excision of the scalp lesions with preservation of the periosteum. [Figure 3]. Split-thickness skin grafting was performed 15 days later to cover the resulting defects. The postoperative course was uneventful, and complete wound healing was achieved within one month. [Figure 4].

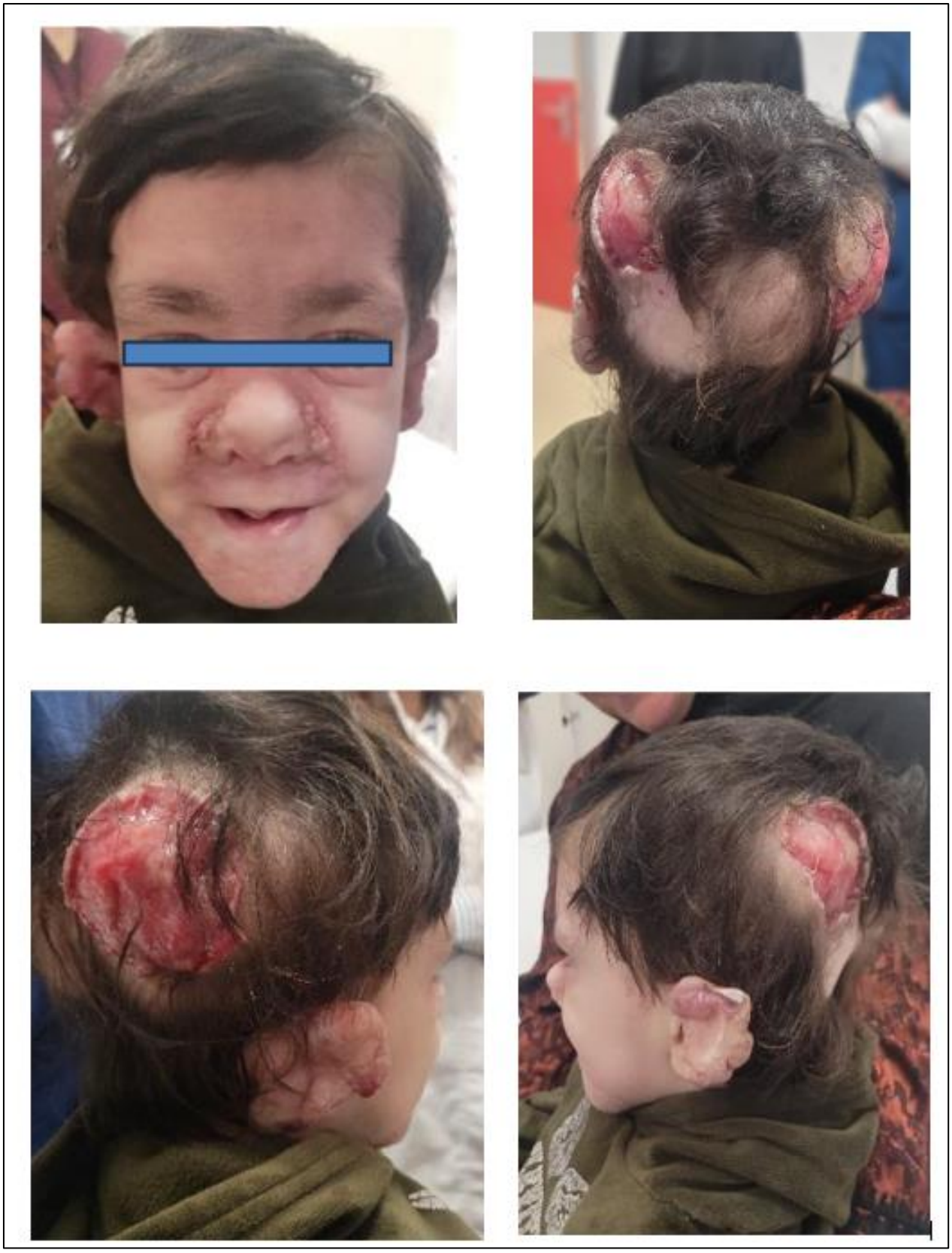

Figure 1 Aspect of lesions

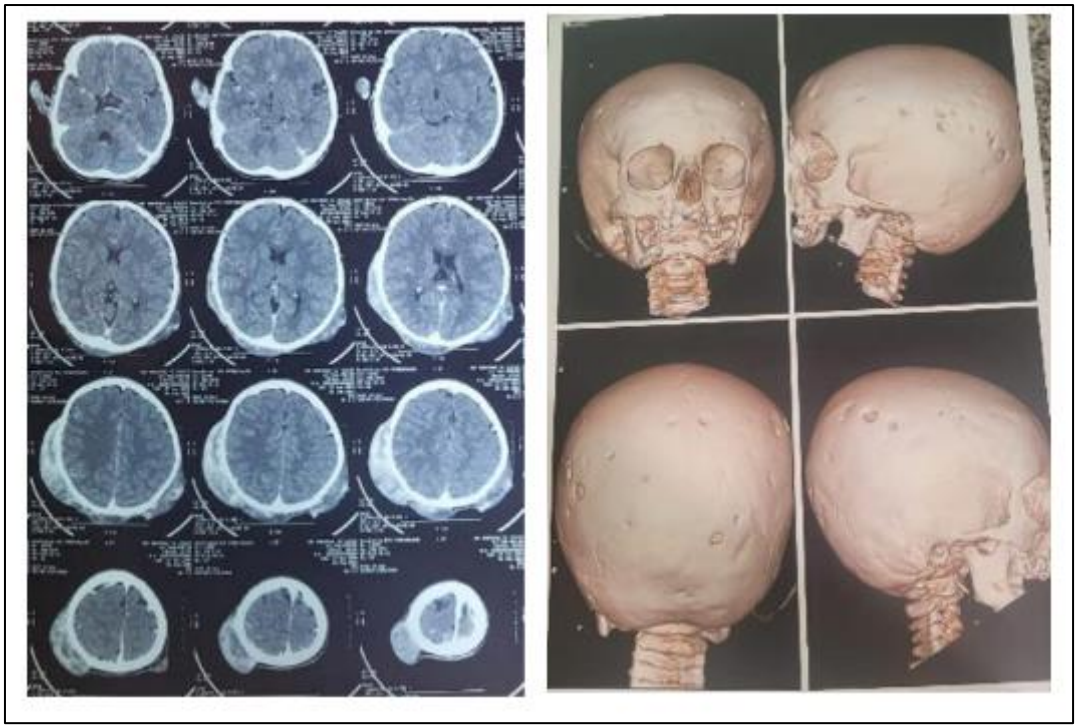

Figure 2 Ct Scan

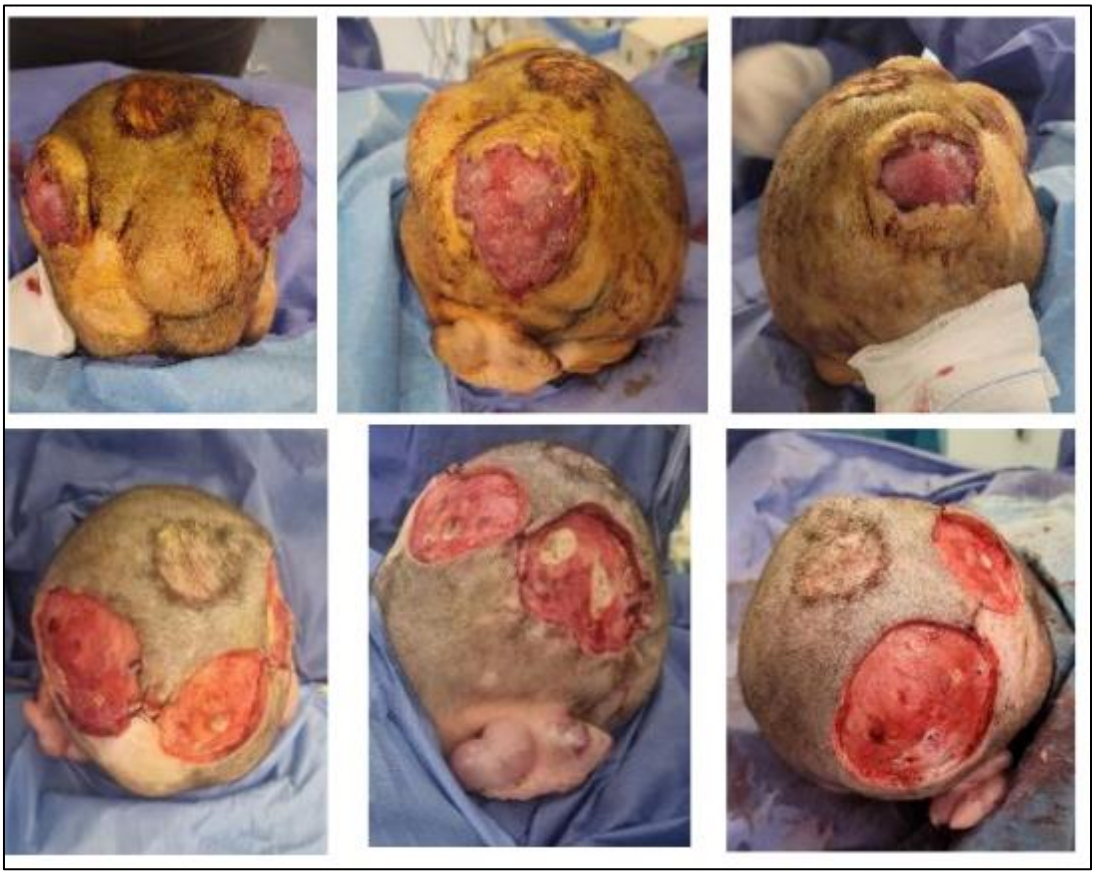

Figure 3 First stage operation (Excision of Scalp lesions)

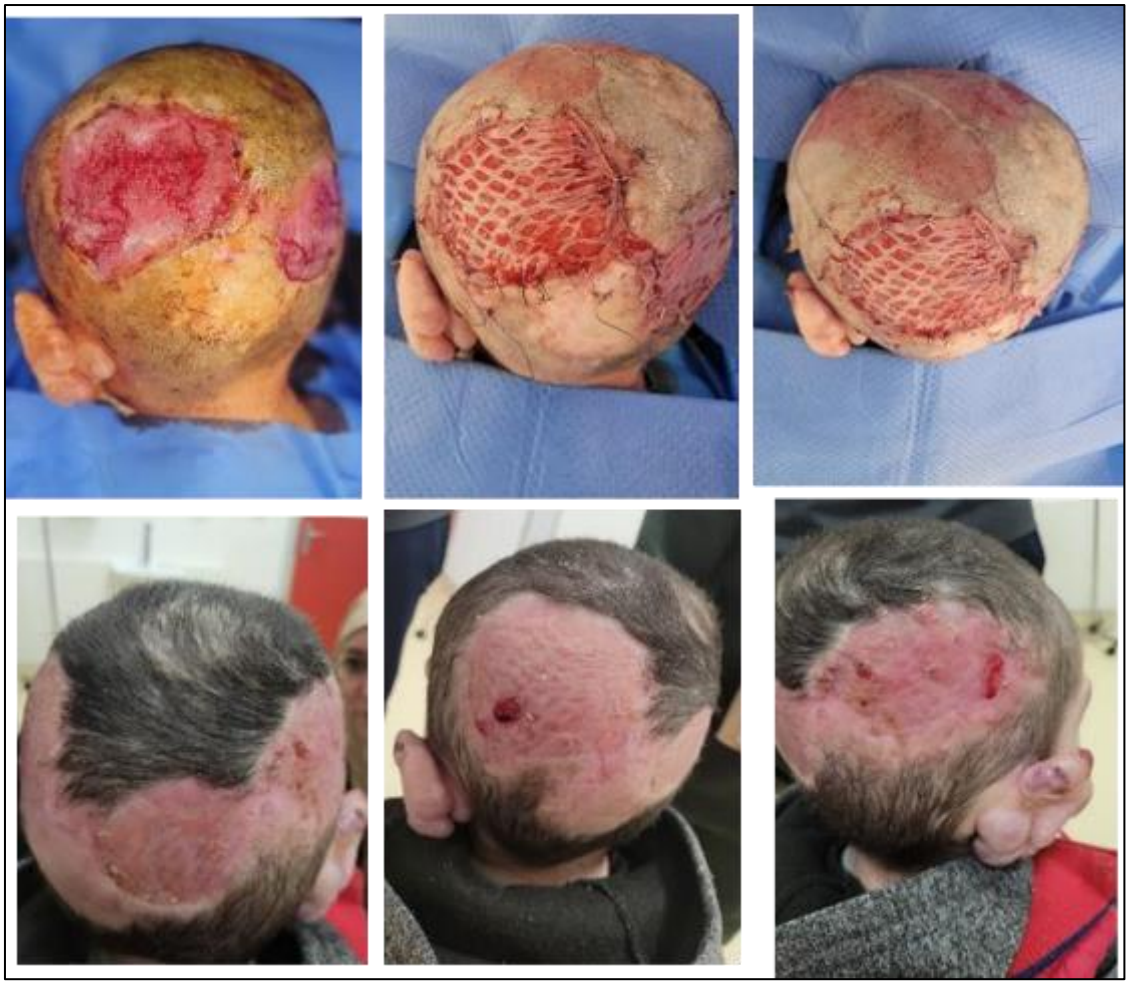

Figure 4 Second stage operation (Split Thickness skin Graft) and final aspect after healing

3. Discussion

Infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF) were long described as two distinct clinical entities [2]. However, in 2003, Dowling et al. and Hanks et al. demonstrated that these two conditions actually belong to the same pathological continuum following the identification of mutations in the capillary morphogenesis gene 2 (*CMG2*), located on chromosome 4q21 [5]. Due to this phenotypic continuity and the variability of clinical expression, the generic term "hyaline fibromatosis syndrome" (HFS) has been proposed [13].

Joint contractures, papular and nodular skin lesions, gingival hyperplasia, osteopenia, and normal neurocognitive development are shared clinical features of both ISH and JHF. ISH typically manifests early, within the first six months of life, and often follows a fatal course before the age of two, most commonly due to severe infections or chronic diarrhea. Conversely, JHF has a later onset during early childhood or infancy, with generally less severe symptomatology, allowing for survival into the second or third decade. Characteristic manifestations of ISH include skin thickening associated with erythema or hyperpigmentation over bony prominences, visceral involvement, persistent diarrhea, severe recurrent infections, and growth retardation.

Patients with JHF, on the other hand, tend to present with larger cutaneous nodules, frequently localized on the scalp [6]. Our patient exhibited overlapping clinical features of both forms, including the early appearance of clustered fleshy papular lesions on the nose, ears, and gluteal region, associated with larger scalp nodules, joint contractures, and chronic diarrhea.

The pathophysiology of hyaline fibromatosis syndrome remains incompletely elucidated. It has been suggested that excessive synthesis of glycosaminoglycans by fibroblasts may be involved [3]. Deletion mutations of the *CMG2* gene, also known as anthrax toxin receptor 2 (*ANTXR2*), have been identified in both ISH and JHF patients. *CMG2* is an integrin-

type transmembrane receptor that plays a role in cell–matrix interactions, basement membrane integrity maintenance, and endothelial cell morphogenesis [7]. Missense or in-frame mutations affecting the cytoplasmic domain are generally associated with JHF, whereas truncating mutations or missense mutations affecting the extracellular ligand-binding domain are more frequently responsible for ISH [2]. Although consanguinity is frequently reported in family histories, it is neither constant nor essential for the diagnosis of ISH or JHF in a suggestive clinical context.

Histologically, the lesions are characterized by the presence of fibroblasts embedded in a PAS-positive hyaline material. Cellularity varies and is inversely correlated with the extent of hyaline deposits. The accumulation of this material within the dermis is progressive and persistent, leading to the evolution of lesions from simple papules to nodules or tumor-like masses, which may undergo ulceration and secondary infection. The differential diagnosis for hyaline fibromatosis syndrome notably includes congenital generalized fibromatosis, Farber lipogranulomatosis, lipoid proteinosis, mucopolysaccharidoses, and Winchester syndrome [8].

Therapeutic management is essentially symptomatic. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics may be used for pain control, while physiotherapy is recommended when passive joint mobilization is painful. Most treatments proposed for ISH have not demonstrated lasting efficacy. Surgical excision of large tumors may be considered, although recurrences are frequent. Improvements in joint mobility and flexibility have been reported with oral D-penicillamine. Gingival hyperplasia can be managed with partial gingivectomy. Parenteral antibiotic therapy and close monitoring of fluid and electrolyte balance may be necessary. Therapeutic trials including dimethyl sulfoxide, ketotifen, and calcitriol have also been reported [4].

It should be emphasized that cognitive functions are preserved in these patients. Therefore, early diagnosis, appropriate genetic counseling for families, and multidisciplinary follow-up are essential to optimize management and prognosis. In this regard, the term "hyaline fibromatosis syndrome" appears most appropriate to unify ISH and JHF under a single nosological entity.

4. Conclusion

In conclusion, hyaline fibromatosis syndrome is a rare but debilitating condition that should be considered in patients presenting with a triad of cutaneous nodules, gingival hyperplasia, and joint contractures. Although historically divided into juvenile and infantile forms, clinical and genetic evidence now supports a single disease spectrum caused by *ANTXR2* mutations. While cognitive functions remain unaffected, the physical burden is significant, often requiring multidisciplinary care. Early recognition is crucial for providing families with accurate genetic counseling and implementing symptomatic treatments to improve the patient's quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethiacl approval was obtained.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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