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# A Rare Case Report of Hyaline Fibromatosis Syndrome with an Overlapping Phenotype

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## Abstract:

Hyaline fibromatosis syndrome (HFS) is a rare, autosomal recessive condition due to pathogenic variants in the ANTXR2 gene, associated with the deposition of amorphous hyaline material in the skin, connective tissues, soft tissues, and internal organs. There is a clinical spectrum between the severe infantile systemic hyalinosis (ISH) phenotype and the relatively milder juvenile hyaline fibromatosis (JHF) phenotype. Patients can have generalized skin thickening and stiffness, hyperpigmented papules on extensor surfaces and pressure-bearing areas, fleshy perianal nodules, papules on the face, gingival hypertrophy, subcutaneous swellings of the scalp, and progressive joint contractures resulting in marked musculoskeletal disability. Patients with the ISH phenotype often have severe systemic disease, such as chronic diarrhea, frequent infections, and visceral involvement, with poor early childhood survival. The prognosis is poor and there is no specific treatment. We report a case of a 2-year-old female child with HFS who has overlapping clinical features of both ISH and JHF phenotypes. This case illustrates the variable clinical presentation of HFS and emphasizes the need for early diagnosis and multi-disciplinary management of this rare condition, which is rarely reported in the Indian literature.

## Keywords:

Hyaline fibromatosis syndrome, Infantile systemic hyalinosis, Juvenile hyaline fibromatosis

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## Introduction

Hyaline Fibromatosis Syndrome (HFS; OMIM #228600) is a rare autosomal recessive disorder characterized by abnormal deposition of hyaline material in various tissues and organs of the body. The condition includes two previously described entities, juvenile hyaline fibromatosis and infantile systemic hyalinosis, which are now considered part of the same disease spectrum, with infantile systemic hyalinosis representing the more severe phenotype. HFS results from homozygous or compound heterozygous pathogenic variants in the *ANTXR2* gene located on chromosome 4q21.1 [1].

The disease usually manifests during early infancy. Common clinical features include progressive skin thickening, subcutaneous nodules, painful joint contractures, pearly papular lesions over the face, neck, and perianal region, hyperpigmented patches over bony prominences, and gingival hypertrophy. These

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manifestations occur due to continuous accumulation of proteinaceous hyaline material within the dermis and connective tissues. Some patients may also exhibit mild dysmorphic facial features such as coarse facies, macrocephaly, frontal bossing, malformed ears, and a depressed nasal bridge, which often become more prominent with advancing age. The clinical course of HFS is highly variable. Severe cases present early in life with systemic and visceral involvement and are frequently associated with early mortality, whereas milder forms may present later and remain limited to the skin, face, and distal extremities [1].

## Case Presentation

A 2-year-old female child, born of a second-degree consanguineous marriage by normal vaginal delivery with a birth weight of 2.5 kg, presented with joint contractures since birth, multiple waxy erythematous-to-skin-colored papules over the back, buttocks, abdomen, nape of the neck, nose, and pinna for the past 1.5 years, and multiple scalp swellings for the past 2 months. At birth, she had contractures involving both elbow and knee joints. The parents noticed that the child experienced discomfort on handling and had difficulty moving her limbs.

At the age of 3 months, she started developing multiple waxy papules initially over the back, buttocks, and perianal region, which gradually appeared over the abdomen, nape of the neck, nose, and pinna over the subsequent 1 year. By the age of 8 months, the parents also observed gingival overgrowth. Over the past 2 months, she developed multiple cystic swellings over the scalp, which had shown rapid progression in both size and number during the preceding 1 month. There was no similar history in the family. There was no history of recurrent infections or diarrhea.

On examination, three bilateral, nontender, mobile scalp swellings measuring approximately 4 × 3 cm to 6 × 5 cm were noted. The overlying hair and skin appeared normal. The swellings were cystic in consistency with positive fluctuation, and no underlying bony defect was palpable (Figure 1a, 1b). Facial examination revealed a depressed nasal bridge with multiple 1–5 mm asymptomatic, nontender, skin-colored to pink papules clustered over the eyebrows, nose, bilateral nasolabial folds, perioral region, and pinna. In addition, a large erythematous plaque measuring approximately 4 × 3 cm was present over the nose, extending into both nasolabial folds (Figure 2a, 2b).

Multiple small skin-colored papules measuring 0.5–1 cm were also present over the abdomen (Figure 3a). In addition, multiple skin-colored to erythematous papules were noted over the nape of the neck and back (Figure 3b, c). A large erythematous plaque measuring approximately 10 × 5 cm with a smooth, shiny surface was observed over the buttock and perianal region (Figure 3d). Hyperpigmented indurated plaques were present over the bilateral ankles (Figure 4). Flexion contractures involving both elbow and knee joints, resulting in a frog-like posture, were noted (Figure 5a, 5b). Oral examination revealed nodular gingival hyperplasia (Figure 6). Palms and soles demonstrated normal dermatoglyphics, and ophthalmologic as well as otologic examinations were unremarkable.

Deposition disorders, hyalinosis, and stiff skin syndrome were initially considered in the differential diagnosis. Laboratory investigations revealed a hemoglobin level of 11 g/dL and a total leukocyte count of 11,000/mm³, while the remaining biochemical parameters were within normal limits for age. Radiological examination of the skull showed normal bony structures with associated subcutaneous swellings. X-rays of the long bones demonstrated osteopenia, whereas chest radiography and abdominal ultrasonography were unremarkable. Ultrasound evaluation of the scalp lesions revealed superficial fluid-filled swellings without intracranial communication.

Histopathological examination of a papular lesion from the back demonstrated a thickened dermis containing abundant eosinophilic hyaline material (Figure 7a). On higher magnification, a few spindle-shaped cells and mild perivascular inflammatory infiltrates were identified within the hyalinized stroma (Figure 7b). The deposited material showed positivity with periodic acid–Schiff (PAS) staining, appearing magenta-pink

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(Figure 8), while alcian blue and Masson's trichrome stains were negative, thereby excluding mucopolysaccharidosis and collagen deposition disorders.

Based on the clinical presentation and histopathological findings, a diagnosis of Hyaline Fibromatosis Syndrome was confirmed. The patient was advised physiotherapy for management of joint contractures and surgical excision of scalp swellings, along with genetic counseling for the parents.

## Discussion

Hyaline fibromatosis syndrome (HFS; OMIM 228600) is an uncommon autosomal recessive disorder resulting from homozygous or compound heterozygous mutations in the *ANTXR2* gene, also known as capillary morphogenesis protein-2 (CMG2), located on chromosome 4q21 [2]. The disease spectrum includes infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF), which are currently regarded as phenotypic variants of the same genetic disorder [2]. HFS has been reported predominantly among individuals of Arab ethnicity, with fewer than 70 cases of JHF and less than 20 cases of ISH documented worldwide [3].

The exact composition and origin of the deposited hyaline material remain uncertain. Possible mechanisms involve focal accumulation of glycosaminoglycans and hyaluronic acid, as well as abnormalities of collagen metabolism, including lack of pro-alpha2 collagen chain and type III collagen, with an increase in synthesis and a decrease in degradation of type I collagen [3].

Affected infants are generally normal at birth, with clinical manifestations appearing during the early months of life. Progressive flexion contractures of large joints gradually develop, often resulting in a characteristic frog-like posture with impaired ability to stand or ambulate [4]. Facial dysmorphism may include deep-set eyes, a depressed nasal bridge, frontal prominence, and a box-shaped skull configuration. Cutaneous manifestations typically comprise papulonodular lesions, gingival enlargement, and hyperpigmented thickened patches or plaques over pressure points and bony prominences [5]. Radiographic evaluation of long bones may reveal delayed bone maturation, marked osteopenia, osteolytic erosions, and radiolucent defects.

Infantile systemic hyalinosis (ISH) differs from juvenile hyaline fibromatosis (JHF) by the presence of widespread visceral hyaline deposition, recurrent infections, protein-losing enteropathy, failure to thrive, and early mortality, usually within the first three years of life, with recurrent respiratory infections representing the most frequent cause of death [2]. Laboratory abnormalities may include hypochromic microcytic anemia, hypoalbuminemia, leukocytosis, and thrombocytosis, while intellectual development is generally preserved [5].

In the present case, a 2-year-old child exhibited characteristic features of HFS, including bilateral elbow and knee flexion contractures with a frog-like posture, papulonodular skin lesions, gingival hyperplasia, and hyperpigmented plaques over pressure-bearing areas. Multiple papules and shiny erythematous plaques involved the face, trunk, neck, back, and perianal region, alongside multiple bilateral cystic scalp swellings without underlying bony defects. Despite early onset and marked cutaneous and musculoskeletal involvement, the absence of recurrent infections, persistent diarrhea, failure to thrive, and visceral involvement suggested an intermediate phenotype within the HFS spectrum, sharing features of both ISH and JHF.

Clinical differentials include congenital generalized fibromatosis, nodular amyloidosis, Farber disease, Winchester disease, mucopolysaccharidosis, neurofibromatosis, and neonatal onset multisystem inflammatory disease (NOMID) [6, 7]. Histopathology or electron microscopy of skin tissue is needed to establish the diagnosis. Histopathological examination of a typical papulonodular skin lesion shows deposition of an amorphous hyaline, eosinophilic substance in which spindle-shaped cells are embedded. It may be vaguely chondroid. The material is PAS positive

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and diastase resistant and does not stain with alcian blue [8].

Intestinal biopsy may demonstrate villous atrophy and lymphangiectasia. Skeletal X-rays may reveal osteopenia, periosteal reaction, and lucent lesions. Treatment has been unsatisfactory. Penicillamine has been tried with limited success. There are anecdotal reports of the use of methotrexate, calcitriol, dimethylsulfoxide, and ketotifen. Early surgical excision is recommended by a few authors to prevent new lesions in JHF, but recurrences are frequent. Physiotherapy is advocated for muscle strength and treating contractures. Treatment of infections is necessary [2, 9]. Genetic counseling includes informing the parents that at conception, the next child has a 25% chance of being affected [6].

## Declarations

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form the patient's parents/guardians have given their consent for images and other clinical information to be reported in the journal. The parents understand that the patient's name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Conflicts of Interest:** No conflicts to disclose

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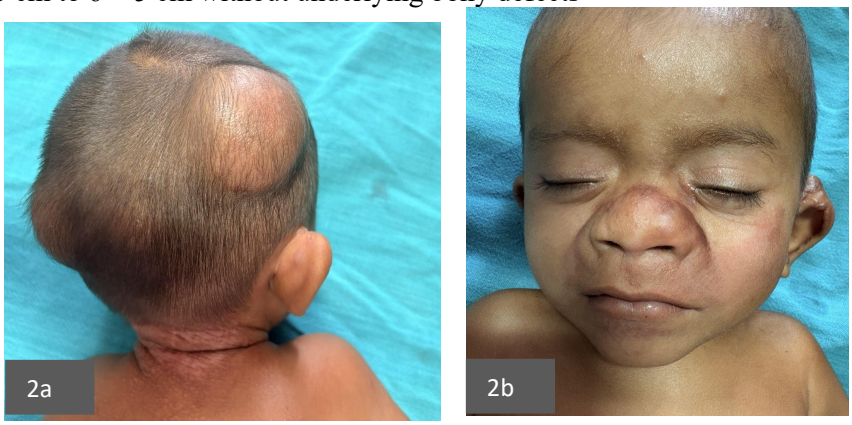
**Figure Legends**


**Figure 1 (a, b):** Three bilateral, nontender, mobile cystic scalp swellings measuring approximately 4 × 3 cm to 6 × 5 cm without underlying bony defects



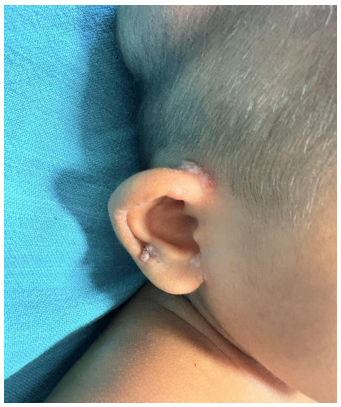



**Figure 2 (a, b):** Facial examination revealing a depressed nasal bridge, a large erythematous plaque (4 × 3 cm) over the nose extending into both nasolabial folds, and multiple 1–5 mm asymptomatic, skin-colored to pink papules clustered over the eyebrows, nose, perioral region, and pinna.

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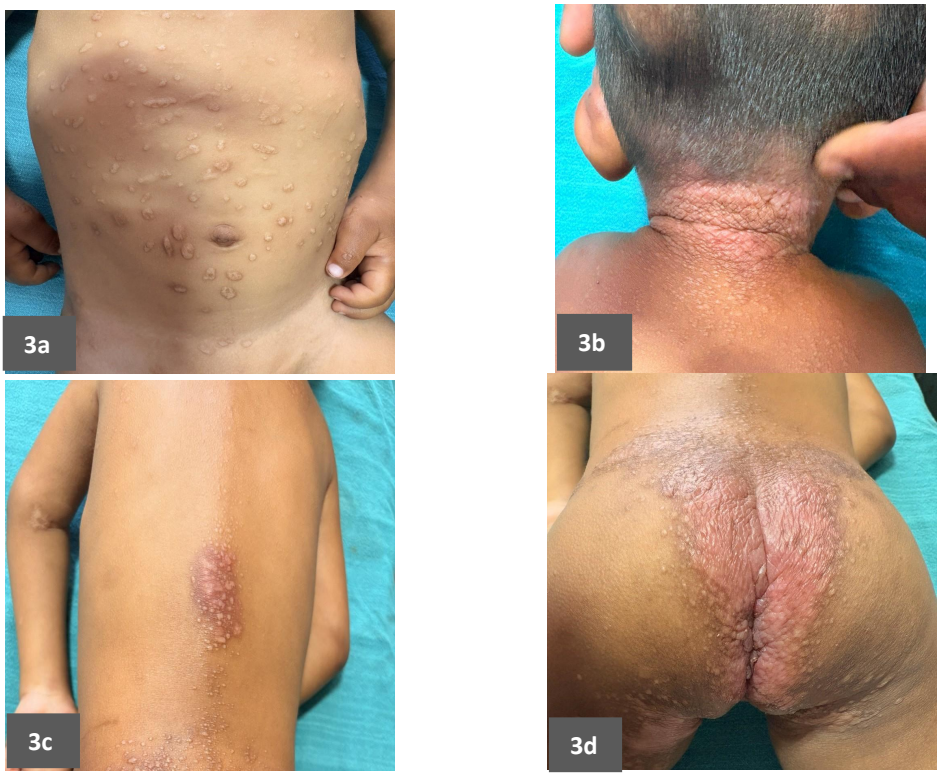


**Figure 3 (a, b, c, d):** Multiple small skin-colored papules (0.5–1 cm) over the abdomen (a), nape of the neck, and back (b, c). A large erythematous plaque (10 × 5 cm) with a smooth, shiny surface over the buttock and perianal region (d).

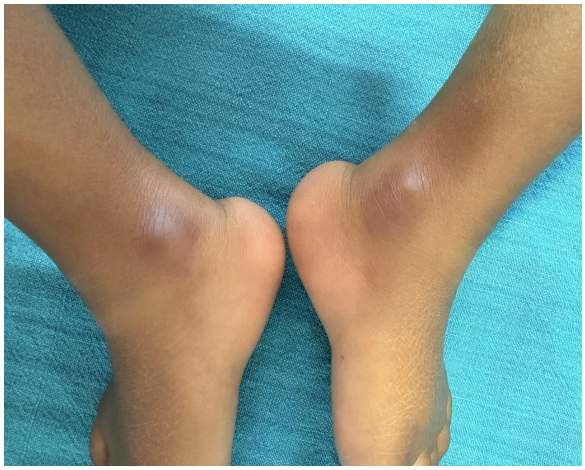

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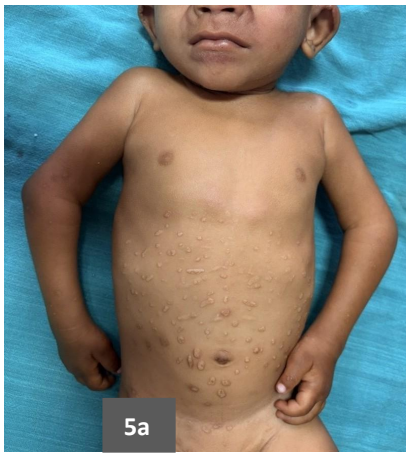
**Figure 4:** Hyperpigmented indurated plaques over the bilateral ankles.
Hyperpigmented indurated plaques over bilateral ankle **(figure 4)**



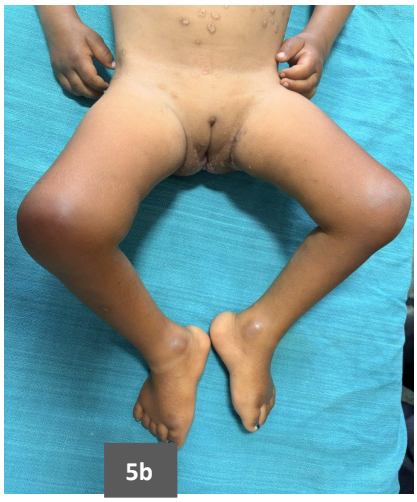




**Figure 5 (a, b):** Flexion contractures involving both elbow and knee joints, resulting in a characteristic frog-like posture.

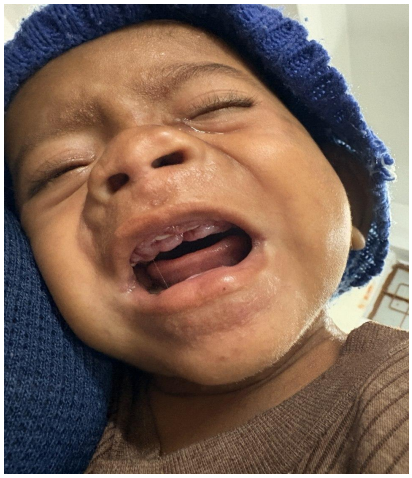


**Figure 6:** Oral examination revealing nodular gingival hyperplasia.

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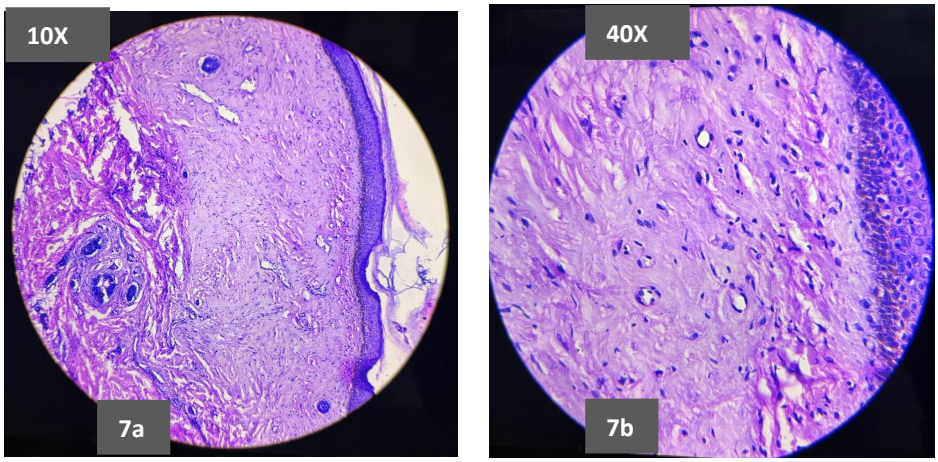


**Figure 7 (a, b):** Histopathology (H&E, 10X) demonstrating a thickened dermis containing abundant eosinophilic hyaline material (a). On higher magnification (H&E, 40X), a few spindle-shaped cells and mild perivascular inflammatory infiltrates are identified within the hyalinized stroma (b).

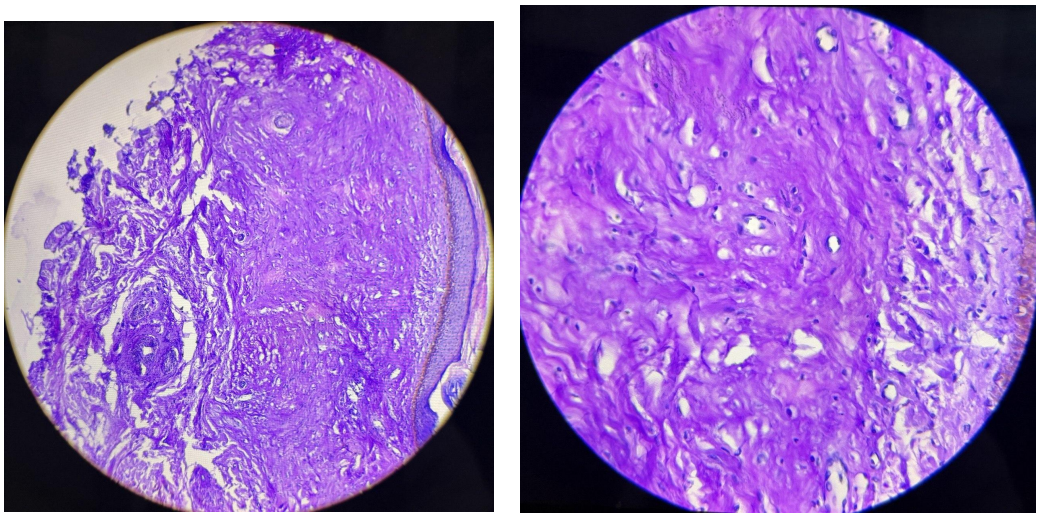

**Figure 8:** Hyaline material staining magenta-pink, confirming positivity and diastase resistance (Periodic acid–Schiff stain, 10X and 40X).