Abstract
Hyaline fibromatosis syndrome (HFS) is rare autosomal recessive disease characterized by the deposition of amorphous hyaline material in skin and visceral organs. It represents a disease spectrum with infantile systemic hyalinosis (ISH) being the severe form and juvenile hyaline fibromatosis (JHF) being the mild form. Dermatologic manifestations include thickened skin, perianal nodules, and facial papules, gingival hyperplasia, large subcutaneous tumors on the scalp, hyperpigmented plaques over the metacarpophalangeal joints and malleoli, and joint contractures. ISH shows a severe visceral involvement, recurrent infections, and early death. We report a case of 2.5-year-old female patient who presented with HFS who had overlapping features of both ISH and JHF. To the best of our knowledge, very few cases of HFS have been reported in Indian literature till date.

Key Words: Hyaline fibromatosis syndrome, infantile systemic hyalinosis, joint contractures, juvenile hyaline fibromatosis, nodules on scalp

Introduction
Hyaline fibromatosis syndrome (HFS, Online Mendelian Inheritance in Man 228600) is a rare autosomal recessive condition characterized by deposition of amorphous, hyaline material in skin and visceral organs.[1] Infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF) are two variants of HFS. ISH is distinguished from JHF by hyaline deposits in multiple organs, recurrent infections, and death within the first 2 years of life.[1]

Case Report
A 2.5-year-old female patient born of second-degree consanguineous marriage and normal full-term vaginal delivery presented with four painless swellings over scalp of 6 months duration slowly increasing in size along with raised lesions over face and perianal region of 5 months duration increasing in number. She had fever, cough, and cold for 6 days duration with history of recurrent hospital admissions in the past for bronchopneumonia and diarrhea. Her mother gave a history of inability to move limbs over the past 1 year and inability to stand and walk till date. There was no similar history in siblings, parents, or other family members.

On examination, four bilateral, nontender, and mobile swellings of sizes ranging from 4 cm × 5 cm to 7 cm × 6 cm were seen over scalp [Figure 1]. Hair loss was present. They were cystic in consistency with positive fluctuation and transillumination. Surface of one swelling showed hemorrhagic crusting and bleeding [Figure 1c]. There were no underlying bony defects palpated. Regional lymphadenopathy was absent. Face showed depressed nasal bridge with multiple 1–5 mm asymptomatic nontender skin colored to pink papules clustered over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2]. Similar multiple, tiny, shiny, pink, moist papules were seen around anal orifice. A pink, fleshy, linear plaque of size 1–5 cm was seen in natal cleft and lower back [Figure 3]. Polydactyly was present in the left hand with hyperpigmented indurated plaques over bilateral nasolabial folds, nose, perioral area, eyebrows, and pinna [Figure 2].
Palms and soles showed normal dermatoglyphics. Eye and ear examination was normal.

A differential diagnosis of deposition disorder, hyalinosis, and stiff skin syndrome was proposed.

Complete blood count showed hemoglobin (8 g/dL), total leukocyte count of 15,200/mm³ mean corpuscular volume, and decreased mean corpuscular hemoglobin (MCH) concentration and MCH whereas peripheral blood smear revealed microcytic hypochromic anemia. Biochemical investigations were within normal range for age. X-ray of the skull showed normal skull bones with subcutaneous swellings. X-rays of the long bones of limbs showed osteopenia and delayed maturation. Chest X-ray showed bilateral congestion and consolidation. Abdominal ultrasound revealed no major abnormality. Ultrasound of the skull showed superficial fluid filled lesions with no communication with inner side of the skull.

Histopathological examination of papule from perianal region showed thickened dermis with abundant hyalinized eosinophilic ground substance [Figure 5a]. Higher magnification (<400) showed a few spindle cells in abundant hyalinized eosinophilic ground substance with chondroid appearance at few places [Figure 5b]. Hyaline material stained magenta pink with periodic acid–Schiff (PAS) stain [Figure 6] but was negative with alcian blue or Masson’s trichrome stains, thereby ruling out mucopolysaccharidosis and collagen deposition disorder, respectively. Based on clinical and histopathological findings, a final diagnosis of HFS was made. Patient was advised physiotherapy for release of contractures and surgical excision of scalp tumors under care of pediatric surgeon. Genetic counseling of parents was done.
**Discussion**

HFS (Online Mendelian Inheritance in Man 228600) is a rare autosomal recessive condition caused by homozygous or compound heterozygous mutation in the gene encoding capillary morphogenesis protein-2 (CMG2 or ANTXR2) on chromosome 4q21. ISH and JHF are two variants of HFS. Most frequent in Arab with around <70 cases of JHF and <20 cases of ISH were reported worldwide till date. Origin and nature of hyaline material is still unknown. Recent research suggests focal synthesis of glycosaminoglycan and hyaluronic acid. Recently, absent pro-alpha2 collagen chain and an absent collagen Type 3 along with increased synthesis and decreased degradation of Type 1 collagen have been suggested.

Patients are usually normal at birth. Abnormalities begin in the first few months of life with progressive flexor joint contractures causing a frog-like position and inability to stand and walk. Face shows peculiar features such as deep set eyes, depressed nasal bridge, square box head, and prominent forehead. Characteristic skin lesions are papulonodular skin lesions, gingival hypertrophy, and thickened hyperpigmented macules/patches over bony prominences of the joints. Radiological examination of the long bones may show delayed skeletal maturation, severe osteopenia, bony erosions, and lucent defects. ISH is distinguished from JHF by hyaline deposits in multiple organs, recurrent infections, protein-losing enteropathy, failure to thrive, and death within the first 3 years of life recurrent chest infections being the leading cause of death. Hypochromic microcytic anemia, low albumin, moderately elevated white blood cells count, and platelet count may be present. Cognitive development is normal.

Clinical differentials include congenital generalized fibromatosis, nodular amyloidosis, Faber’s disease, Winchester disease, mucopolysaccharidosis neurofibromatosis, neonatal onset multisystem inflammatory disease (NOMID). 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 and diastase resistant and does not stain with alcian blue. 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 use of methotrexate, calcitriol, dimethylsulfoxide, ketotifen. Early surgical excision is recommended by 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.

Genetic counseling includes informing the parents that at conception next child has a 25% chance of being affected.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.
Conflicts of interest
There are no conflicts of interest.

What is new?
HFS is a relatively new term coined recently to include cases of ISH, JHF, and intermediate cases with overlapping features of both. This case is being reported for its rarity in India.

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