JUVENILE HYALINE FIBROMATOSIS- REPORT OF A RARE CASE WITH SUBCUTANEOUS NODULES AS THE SOLE MANIFESTATION

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ABSTRACT

BACKGROUND

Juvenile Hyaline Fibromatosis (JHF) is a rare autosomal recessive connective tissue disorder with distinct clinical and histopathological features. Approximately, 70 cases of JHF have been reported worldwide with only a handful of cases from India. Herein, we report a case of JHF in a middle-aged man whose sole presentation was multiple variably-sized painless nodules over the entire body since childhood with history of repeated surgical excision for the same. Histopathology revealed proliferation of fibroblasts lying in a background of PAS positive amorphous hyaline ground substance. The genetic basis of this disorder was recently mapped, which led to the basis of aberrant synthesis of glycosaminoglycans and disordered collagen metabolism. JHF has a relentlessly progressive course with no specific treatment available till date.

KEYWORDS

Juvenile Hyaline Fibromatosis, Subcutaneous Nodules, Autosomal Recessive, Capillary Morphogenesis Protein 2.

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BACKGROUND

Juvenile Hyaline Fibromatosis (JHF) is an extremely rare and progressive hereditary disease that usually affects more than one sibling in the family with typical onset in infancy or early childhood.[1] The present name, JHF was coined by Kitano in 1976.[2] It is characterised by papulonodular skin lesions, gingival hypertrophy, joint contractures and bone involvement in variable degrees. Identification of characteristic histopathological features in biopsy of skin nodules is the hallmark in confirming the diagnosis.[3] Recent studies have identified Capillary Morphogenesis Protein 2 (CMG2) mutation encoded by a gene on chromosome 4q21 to be the causative factor.[4] We report this case due to the rarity of the disorder and to the best of our knowledge, the first case in literature where JHF presented with subcutaneous nodules as the sole manifestation with no other associated manifestations so far in an adult man. The clinical presentation, genetic basis, histopathological findings, differential diagnosis and treatment options have been discussed and literature reviewed.

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CASE REPORT

A 47-year-old man born of second-degree consanguineous marriage presented with multiple variably sized painless papulonodular skin lesions over the head, neck and both upper and lower extremities. Repeated surgical excisions of the recurring cutaneous lesions from various sites were done since childhood. He was otherwise healthy with normal mental function and no systemic symptoms. Family history revealed similar disorder in his elder brother and cousins. Skin examination showed multiple discrete and confluent firm, nontender erythematous to hyperpigmented nodules of varying sizes over the forehead, left upper eyelid, right alae nasi, forearm, dorsum of hands, palms, heels and soles [Figure 1-3]. There were no cafe au lait spots, axillary freckles, bone lesions, joint contractures or gingival hypertrophy. Rest of the systemic examination was normal. Routine laboratory investigations, echocardiogram, radiological findings and ultrasonography of the abdomen were normal. Surgical excision of the subcutaneous nodule on the forehead was done. Histopathology revealed an irregular dermal lesion [Figure 4] composed of benign fibroblastic cell proliferation widely embedded in an abundant amorphous eosinophilic hyaline matrix [Figure 5 and 6]. The hyaline ground substance showed PAS positivity. Based on the characteristic clinical presentation and histopathological findings, the man was diagnosed to have Juvenile Hyaline Fibromatosis (JHF).

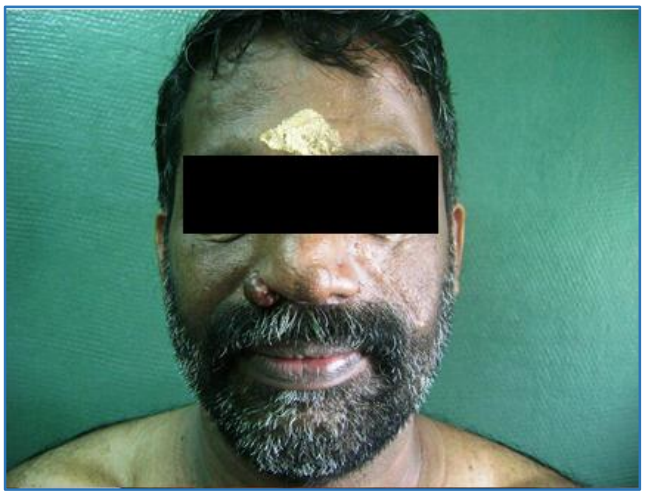

Figure 1. Multiple Subcutaneous Nodules over the Forehead, Medial Aspect of Left Eyelid and Right Ala Nasi

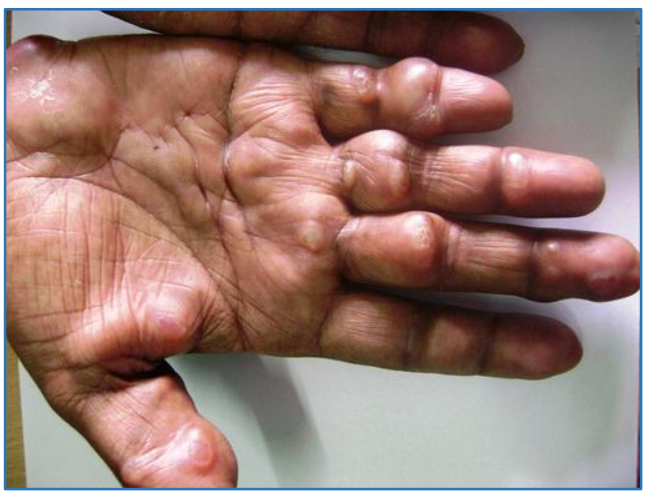

Figure 2. Multiple Discrete and Confluent Translucent Nodules over the Palm

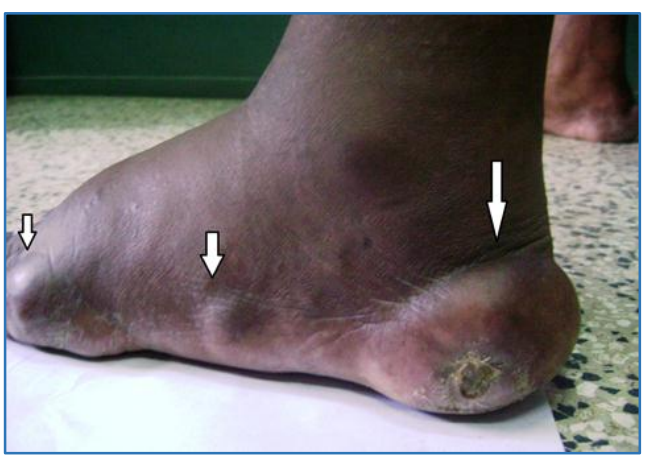

Figure 3. Multiple Subcutaneous Nodules of Varying Sizes Over the Lateral Aspect of Foot and Heel (Arrow Heads)

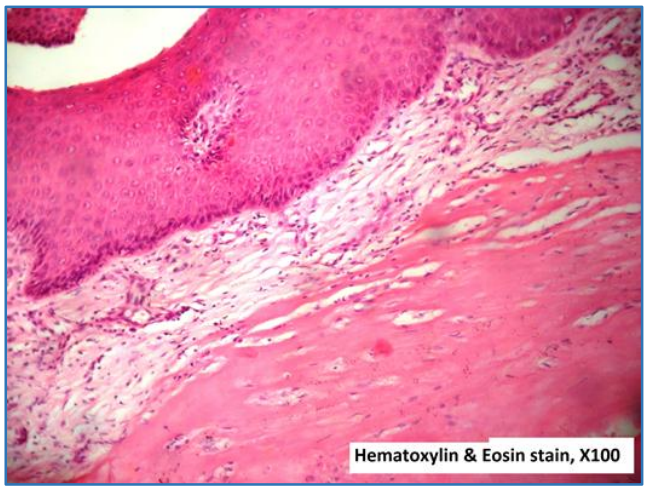

Figure 4. Microscopic Picture Showing a Poorly-Circumscribed Dermal Lesion

Figure 5. Dermal Lesion Composed of Proliferated Benign Spindle-Shaped Fibroblasts in a Background of Abundant Deposition of Homogenous Hyaline Material

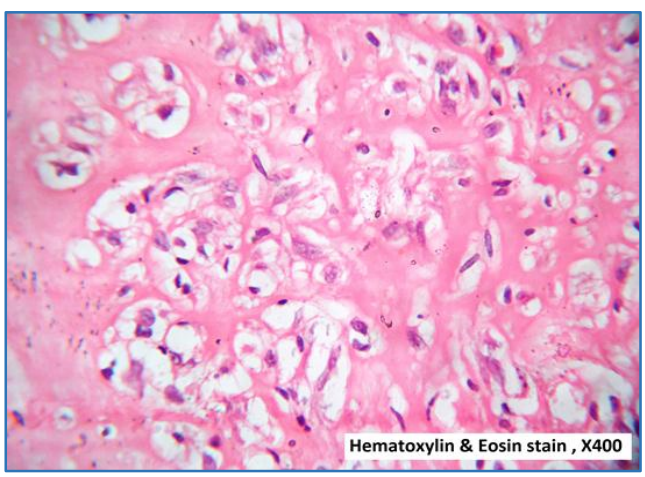

Figure 6. High power Showing Proliferated Fibroblasts Interspersed with Abundant Hyaline-Like Material

DISCUSSION

Juvenile hyaline fibromatosis is a crippling disorder of the connective tissue characterised by abnormal growth of hyalinised fibrous tissue that determines the appearance of skin lesions and the involvement of other organs.[5] It was originally described way back in 1873 by Murray as "Molluscum fibrosum."[2,6] Most cases have an autosomal recessive mode of inheritance with a typical onset in early childhood with slight male preponderance[7] like in this particular case. JHF is defined clinically by a constellation of clinical findings that include pearly skin papules or subcutaneous firm nodules, joint contractures, acral osteolytic lesions, gingival hypertrophy along with normal intelligence.[3,5,6] Gilaberte et al proposed the clinical criteria for JHF [Table 1].[8] All the clinical manifestations of typical juvenile hyaline fibromatosis need not necessarily be present in each patient.[1] Our present case had only multiple subcutaneous nodules so far with no other associated clinical manifestations, which were quite unique and the first to be reported in literature to date. The skin lesions were slow growing, painless papulonodular lesions of varying sizes located particularly around the nostrils, ears, paranasal folds, scalp, limbs and perianal regions. He did not have gingival hypertrophy, joint contractures or bone involvement. Musculoskeletal involvement is the most debilitating problem in JHF as most children and adults become bedridden and die of infection.[9]

Table 1 shows the clinical criteria for Juvenile Hyaline Fibromatosis.

Major Criteria	Skin lesions, Gingival Hypertrophy
Minor Criteria	Osteolytic Erosions, Joint Contractures

Table 1

The aetiology of JHF is still unclear, but most theories attribute the lesions of JHF to the impaired collagen synthesis, which is thought to be the major pathogenic mechanism. In 2002, Rahman et al provided strong evidence that mutation of the Anthrax Toxin Receptor 2 (ANTXR2) gene, also known as the Capillary Morphogenesis Protein Gene-2 (CMG2) located on chromosome 4q21 is responsible for this disorder.[10] Hanks et al suggested that a defect in ANTXR2 lead to extravasation of hyaline material through the basement membrane into the perivascular space that explained the histological findings in JHF.[11,12] A definitive diagnosis of JHF is based on the histologic findings of skin lesions. The hallmark of this condition is the presence of abundant deposition of homogeneous hyaline matrix that are accompanied by the proliferation of fibroblasts without atypia.[3,6]

The differential diagnosis of JHF includes infantile systemic hyalinosis (ISH), Winchester syndrome, Gingival fibromatosis, Nodular amyloidosis, Congenital generalised fibromatosis, Lipoid proteinosis and Neurofibromatosis.[5,13] ISH includes diffuse skin thickening, hyperpigmented plaques on bony prominences, diarrhoea, frequent severe infections and a fatal outcome. Winchester syndrome is characterised by short stature, generalised osteoporosis, contractures of small joints and corneal opacities with no skin nodules. Gingival fibromatosis is limited to the gingiva and the lesions typically consist of connective tissue that is rich in collagen I and congenital generalised fibromatosis is characterised by multiple dermal and subcutaneous nodules, visceral involvement and death shortly after birth.[3]

The clinical course of JHF is variable and relentlessly progressive. To date, there is no specific treatment for this disorder. Surgical excision is the main therapeutic strategy for JHF and is intended to achieve functional and aesthetic improvements, although there is a high risk for recurrence.[14] The primary treatment for the skin and oral lesions is early surgical excision, but relapses are common. Gingivectomy may provide only short-term benefit and maintenance of good oral hygiene are essential to prevent oral infection in patients with JHF. Joint contractures are treated with intralesional systemic steroids, physiotherapy and/or capsulotomy.[5] Further research is needed to improve treatment in order to help these patients. Genetic counselling is of great importance as the risk of recurrence is 25% in any future pregnancy.[15]

CONCLUSION

To conclude, JHF is a hereditary disease with progressive course and should be highly suspected in an individual with early onset of papulonodular skin lesions associated with/without joint contractures and gingival hypertrophy. Characteristic histopathological features can confirm the diagnosis. Proper multidisciplinary management and regular follow up for the observation of complications are highly crucial in an attempt to slow the progression of this rare disabling disease. This case has been reported due to its rarity in the Indian subcontinent and to emphasise the fact that JHF can present with only subcutaneous nodules without any associated manifestations and hence must be considered by the treating physician in the differential diagnosis of a young individual presenting with multiple subcutaneous nodules.

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