Case Study

A Rare Case of Infantile Systemic Hyalinosis with Mutation in ANTXR2

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ABSTRACT

Infantile systemic hyalinosis is an autosomal recessive rare disorder characterized by progressive joint contractures, skin abnormalities and systemic deposition of hyaline material in many tissues. We report a three month old male child who presented with multiple joint contractures, mild gingival hypertrophy and hyperpigmented skin lesions over both hands and legs. His elder brother child also had similar findings which were progressive and he died at five years of age. Genetic testing in our patient revealed a homozygous single base deletion in the ANTXR2 gene; confirming the diagnosis of Infantile systemic hyalinosis. No specific treatment is available for infantile systemic hyalinosis. Child was treated with supportive therapy with orthopedic support. Early diagnosis of Infantile systemic hyalinosis needs an awareness of this condition which can be confirmed by genetic testing.

Keywords: Hyalinosis, Skin involvement, ANTXR2

INTRODUCTION

Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disease of the connective tissue characterized by generalized deposition of hyaline material in various tissues such as skin, joints, gastrointestinal tract, adrenals, skeletal muscles, gingiva and other organs[1,2,3]. Gene mutations in capillary morphogenesis protein-2 also called as anthrax toxin receptor 2 (CMG2/ANTXR2) gene on chromosome 4q21 are responsible for ISH [4]. Very few case reports of ANTXR2 mutation have been published in Indian population; none from Western part of India [5,6,7,8]. ISH is progressive lethal disease with infants developing repeated purulent infections, diarrhea and osteoporosis in early stages of life. This is followed by hyaline infiltration of the intestinal mucosa causing protein-losing enteropathy which leads to malnutrition. The survival age may vary from two to six years based on management 2. Sepsis, respiratory and cardiac failure are common causes of mortality in these patients [9,10]. We report a rare case ISH with mutation in ANTXR2 gene

CASE DESCRIPTION

A three month old male child, only living issue of a third degree consanguineous marriage was referred to rheumatology clinic with history of excessive crying on being handled with difficulty in moving his limbs and hyperpigmented skin lesions over both hands & legs. There was no history of fever, diarrhea, seizures or failure to thrive. There was history of three unexplained abortions. Older male sibling had similar manifestations and had died due to respiratory illness at the age of five years. Birth history was normal. Neck holding and social smile was present. Anthropometry was within normal limits. Clinical examination revealed absence of obvious dysmorphic facies, flexion contractures over the elbows, wrist, knees, and small joints of the fingers leading to a frog-like position, hyperpigmented indurated plaques on the bony prominences of the metacarpo-phalangeal joints, ankle joints, metatarso-phalangeal joints (Figure 1 and 2), mild gingival hyperplasia with no evidence of hepato-splenomegaly. Hemoglobin (Hb=11.9 gm/dl, WBC=7,200/cmm; N=52%, L=48%, Platelets=267000) and ESR (12mm at the end of one hour) were within normal limits. Ophthalmology examination and 2d-ECHO were normal. X-ray of the knee joint revealed osteopenia with no erosions. Genetic testing revealed that the sample was homozygous for deletion mutation c.1256delC in exon 15 leading to premature termination of protein ANTXR2; confirming the diagnosis of ISH. Child was treated with supportive therapy with orthopedic support.

DISCUSSION

Common age of presentation of ISH is between the ages of 2 and 5 years with multiple nodular skin lesions, gingival hypertrophy, joint contractures, and osteolytic lesions on imaging[11]. The earliest case report of ISH based from India is two month old male child [7]. Our case was also diagnosed early based on characteristic clinical features of ISH including multiple joint contractures and hyperpigmented indurated plaques over bony prominences on multiple joints. Similar to our child, ICH children are usually normal at birth. The sequence and organ involvement severity in ISH is extremely variable. The most debilitating problem in ISH are progressive flexion contractures causing a frog-like position with inability to stand and walk [12]. This is due to an apparent increase in the amount of collagen type VI [13]. Dysmorphic facial feature might include deep-set eyes, depressed nasal bridge, prominent forehead, and macrocephaly which were not present in our patient. Skin lesions in ICH are variable and may include translucent nodules on pulps of fingers, external portions of ears, and nose or small fleshy pearly papules usually near nasolabial folds, mastoid area, and neck all of which were absent in our patient [14]. However, thickened hyperpigmented plaques over bony prominences of joints are a prominent feature of ISH which was seen over multiple joints in our patient. Gingival hyperplasia present in our patient can lead to poor oral hygiene, poor feeding, and dental infections. Imaging in ISH may reveal delayed skeletal maturation, osteopenia, bony erosions, and osteolytic defects [15]. Hematological manifestations of ISH include low serum albumin, hypochromic, and microcytic anemia with elevated WBC count and platelet count [16]. In our patient, hemogram was within normal limits and X-ray of knee joint revealed osteopenia with no erosions. Parents did not consent for skin biopsy. Characteristic histological findings include cords of oval to spindle-shaped cells within the PAS-positive amorphous eosinophilic matrix, containing abundant hyaline material[17]. ISH diagnosis was confirmed on clinical exome analysis which revealed a homozygous single base deletion in the ANTXR2 gene. Treatment is symptomatic. Early tumor removal for nodular lesions, gingivectomy, and nutritional supplementation for gingival hypertrophy and resulting malnutrition, physiotherapy to prevent flexion contractures and intralesional corticosteroid therapy for established joint contractures are modalities used in ISH. Penicillamine, methotrexate, calcitriol, dimethylsulfoxide, and ketotifen have been tried in few cases with limited success [4, 18]. Genetic counseling is an important aspect of management.

CONCLUSION

Identification of this rare condition by paediatrician is critical to facilitate an early diagnosis which in turn will lead to a betterment of prognosis.

FINANCIAL SUPPORT AND SPONSORSHIP
Nil.

CONFLICTS OF INTEREST
There are no conflicts of interest

FIGURE-1

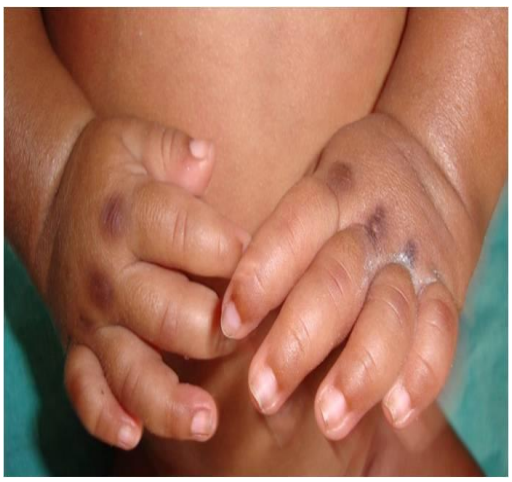

Figure 1: Hyperpigmented indurated plaques on the bony prominences of metacarpo-phalangeal joints

FIGURE 2

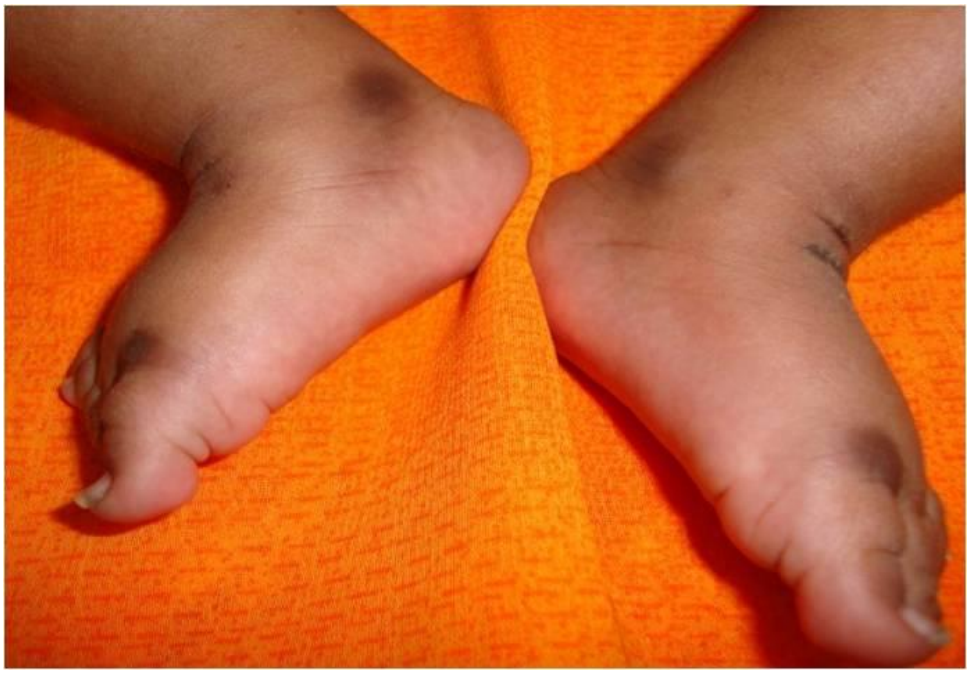

Figure 2: Hyperpigmented indurated plaques on the bony prominences of ankles and metatarso-phalangeal joints

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