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Case Report

H Syndrome: when Cutaneous Signs Provide a Clue to a Multisystemic Genetic Disorder

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ABSTRACT

H syndrome, a rare genetic disorder, is inherited in an autosomal recessive manner. SLC29A3 gene mutation represents the underlying etiology of this syndrome which manifests with various cutaneous and extracutaneous features including hyperpigmentation, sclerosis, hypertrichosis. hyperglycemia, hearing loss, hypogonadism, cardiac anomalies and skeletal deformities.

Keywords: H syndrome; Histiocytosis; Hyperpigmentation

INTRODUCTION

H syndrome is an autosomal recessive genodermatosis which is recently classified within the context of histiocytosis [1]. The name had been suggested due to the fact that most of its features begin with letter "H" as hyperpigmentation, hypertrichosis, hearing loss, hyperglycemia, hypogonadism and hepatosplenomegaly [2].

CASE REPORT

A 17-year old female patient referred to our out-patient clinic (Minia university Hospital, Minia, Egypt) complaining from progressive induration, hyperpigmentation and hypertrichosis over her inner sides of both thighs and legs since she was eleven, she was also complaining from irregular menses and hearing difficulties and there was a positive history of consanguinity.

Examination

Her skin examination revealed bilateral, symmetrical, ill-defined, slightly warm and sclerosed lesions over the medial sides of both thighs and legs. Lesions were associated with evident hypertrichosis (Figure 1)

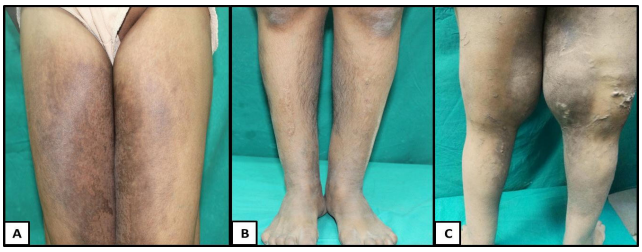

Figure 1: Bilateral symmetrical hyperpigmented plaques (A) on inner sides of thighs (B) on legs with evident hypertrichosis and (C) varicose veins on posterior aspect of lower limbs.

General examination revealed elevated body temperature (38°C), slight exophthalmos, short stature, mild hepatosplenomegaly. Also, skeletal examination revealed flat foot, hallux valgus and flexion contractures of fingers and varicose veins over the posterior aspect of her lower limb (Figure 1 and 2). Psychiatric, neurological and cardiological evaluations were normal.

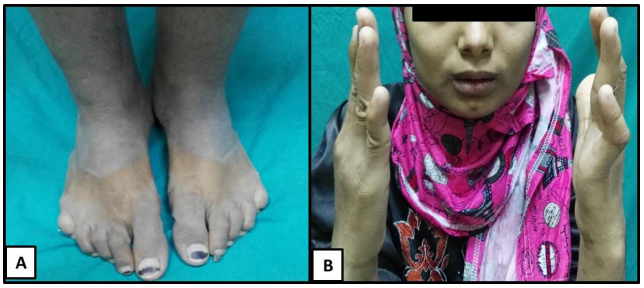

Figure 2: Skeletal deformities in form of (A) Hallus valgus and (B) Flexion contractures of fingers

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Investigations

Laboratory investigations revealed mild microcytic hypochromic anemia, mildly elevated ESR, normal prothrombin time and concentration, normal serum electrolytes, normal blood glucose, normal TSH and low FSH and LH.

Abdominal ultrasound revealed mild hepatosplenomegally and small left ovarian cyst measuring 1x2 cm. Duplex ultrasound of lower limb showed normal deep venous system and increased thickening and echogenicity of skin and subcutaneous tissue with femoral and popliteal lymph node enlargement. Echocardiography was normal. Audiometry revealed features of bilateral sensorineural hearing loss.

A 4 mm punch biopsy was taken and histopathological examination revealed widespread dermal and subcutaneous fibrosis with interstitial histiocytic inflammatory infiltrate admixed with numerous plasma cells, some histiocytes appear vacuolated. Fragmentation of elastic fibers are evident (Figure 3). Based on clinical findings and results of investigations; the case was diagnosed as H syndrome.

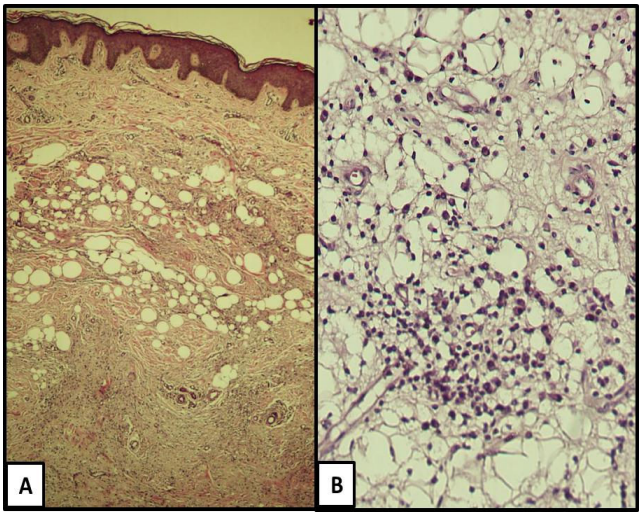

Figure 3: Histopathological examination of skin biopsy by H&E revealed (A) thickened dermis and perivascular and interstitial inflammatory infiltrate (10x) (B) Evident histiocytes and plasma cells (20x).

DISCUSSION

H syndrome is a recently described inherited genodermatosis with a diversity of cutaneous and non-cutaneous manifestations. It is caused by mutations in SLC29A3 gene that encodes for the human equilibrative nucleoside transporter (hENT3) which is a mitochondrial and a lysosomal nucleoside transporter [3]. This mutant hENT3 alter nucleoside uptake by those organelles, mitochondria and lysosomes, with subsequent impairment of their homeostatic functions [3].

The hallmarks of H syndrome are the cutaneous manifestations; therefore, dermatologists are commonly the first to be confronted by such cases in medical practice. Skin manifestations in H syndrome are characteristic and include progressive hyperpigmentation, induration of the inner sides of the thighs that may extend to legs, trunk and genitalia. Also, hypertrichosis is noticeable [4].

On the other side, non-cutaneous manifestations are diverse and almost every organ can be affected in this syndrome. Patients with H syndrome shows wide range of skeletal anomalies as short stature, hallux valgus and flexion contractures of fingers and toes [4]. Patients commonly have insulin-dependent diabetes mellitus (IDDM) which may develop early and solely in this syndrome. However, in some reported cases, IDDM may be developed late or absent [5].

Cardiac anomalies are not uncommon in H syndrome; and echocardiography is mandatory for patients. Other features include febrile episodes, hypogonadism, varicosities, inferior vena cava agenesis, lymphadenopathy and hepatosplenomegaly [4].

Ophthalmologic features in patients with H syndrome may include exophthalmos, dilated lateral scleral vessels, corneal arcus and shallow orbits [6]. Also, H syndrome may feature hematologic abnormalities as anemia or pancytopenia [4].

Differential diagnosis includes mainly POEMS syndrome and Rosaï-Dorfman disease. POEMS syndrome consists of polyneuropathy, organomegaly, endocrinopathy, M protein gammaopathy, and skin changes [7]. Here, POEMS syndrome was excluded due to absence of polyneuropathy, gammopathy and glomeruloid angiomas. Also, Rosaï-Dorfman disease was excluded due to absence of massive painless lymphadenopathy and emperipolesis in skin biopsy [8].

Management is mainly supportive. Oral steroids may temporarily improve cutaneous changes in some patients, but are inappropriate for maintenance due to their side effects. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, has been reported to be effective in a number of patients. Also, azathioprine, methotrexate have been used with a limited success [9].

CONCLUSION

Differential diagnosis includes mainly POEMS syndrome and Rosaï-Dorfman disease. POEMS syndrome consists of polyneuropathy Management is mainly supportive. Oral steroids may temporarily improve cutaneous changes in some patients, but are inappropriate for maintenance due to their side effects Cardiac anomalies are not uncommon in H syndrome; and echocardiography is mandatory for patient

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