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Clinical Progression and Manifestations of H Syndrome: A Case Report of Failed Treatment Option

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 31-year-old
Final Diagnosis: H syndrome
Symptoms: Diabetes milletus • hypothyroidism • sclerodermatous skin changes • sensorineural hearing loss
Clinical Procedure: —
Specialty: Dermatology • Endocrinology and Metabolic • Immunology

Objective: Congenital defects/diseases

Background: H syndrome is an autosomal recessive disorder of histiocytic proliferation with clinical spectrum of unique cutaneous and systemic manifestations. There is no consistent treatment for the disease, and all available options are based on case reports. Here, we present the chronological progression of a case of H syndrome with typical cutaneous manifestations that was misdiagnosed early as meningitis-induced sensorineural hearing loss and later as a non-defined autoimmune connective tissue disease. A new tried, although failed, treatment option is described as well.

Case Report: A 31-year-old Saudi woman born of a consanguineous marriage presented to our dermatology clinic with symmetrical indurated hyperpigmented to violaceous plaques over the medial thighs, upper legs, lower back, volar wrists, and upper arms, associated with hypertrichosis. Hallux valgus of the big toes was clinically detected as well. She had a history of sensorineural deafness, diabetes mellitus, chronic anemia, and hypothyroidism. Genetic analysis of the patient showed a homozygous frameshift pathogenic variant of the SLC29A3 gene, c.243del p.(Lys81Asnfs*20). Systemic treatments in the form of methotrexate and imatinib had been tried; however, both failed to control her sclerotic cutaneous changes.

Conclusions: Knowing the early life presentation and the variable clinical symptoms of H syndrome is crucial in early intervention and further prevention of the non-reversible changes. Moreover, avoiding unnecessary immunosuppressive medication use is warranted in certain circumstances.

Keywords: Histiocytosis with Joint Contractures and Sensorineural Deafness • Histiocytosis • Imatinib Mesylate • SLC29A3 Protein, Human

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/944198

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Introduction

Since its description in 2008 [1], H syndrome has been increasingly reported in the literature. To date, more than 134 cases have been described, mainly of patients from Arab descent [2]. It is an autosomal recessive disorder of histiocytic proliferation with a clinical spectrum of unique cutaneous and systemic manifestations. Hyperpigmented sclerotic skin changes of the inner thighs associated with hypertrichosis are pathognomonic of the disease and are considered the most common feature that characterize the syndrome [3,4]. Apart from its cutaneous sclerotic changes, its clinical mimickers are either in the spectrum of histiocytoses, such as Rosai Dorfman and Erdheim Chester disease [5], or what is importantly described in our case, in the spectrum of rheumatologic/immune-inflammatory disorders [2]. Previous reports, including of monozygotic twins, failed to identify a genotype-phenotype correlation for the disease spectrum, suggesting environmental modifiers being a likely explanation [6,7]. There is no consistent treatment for the disease, and all available options are based on case reports. However, most of the tried modalities failed to control the symptoms [6]. Here, we present a case of H syndrome with typical cutaneous manifestations that was early misdiagnosed as meningitis-induced sensorineural hearing loss and later misdiagnosed as a non-defined connective tissue disease. We further describe the chronologic progression of the disease and a newly tried, although failed, treatment option. Moreover, we emphasize the importance of properly identifying and early diagnosing the syndrome, where the patient can avoid exposure to aggressive non-effective immune-suppressive medications.

Case Report

A 31-year-old Saudi woman born of a consanguineous marriage presented to our dermatology clinic with concerns of pigmented skin lesions since her childhood. The lesions started in the proximal lower limbs, extending to the lower back and distal limbs, and finally to the arms and chest. She was healthy until the age of 6, when she developed what was presumed to be meningitis induced-bilateral sensorineural hearing loss, which was managed with cochlear implantation. After that, she developed insulin-dependent diabetes mellitus, chronic anemia, and primary hypothyroidism. She underwent a bone

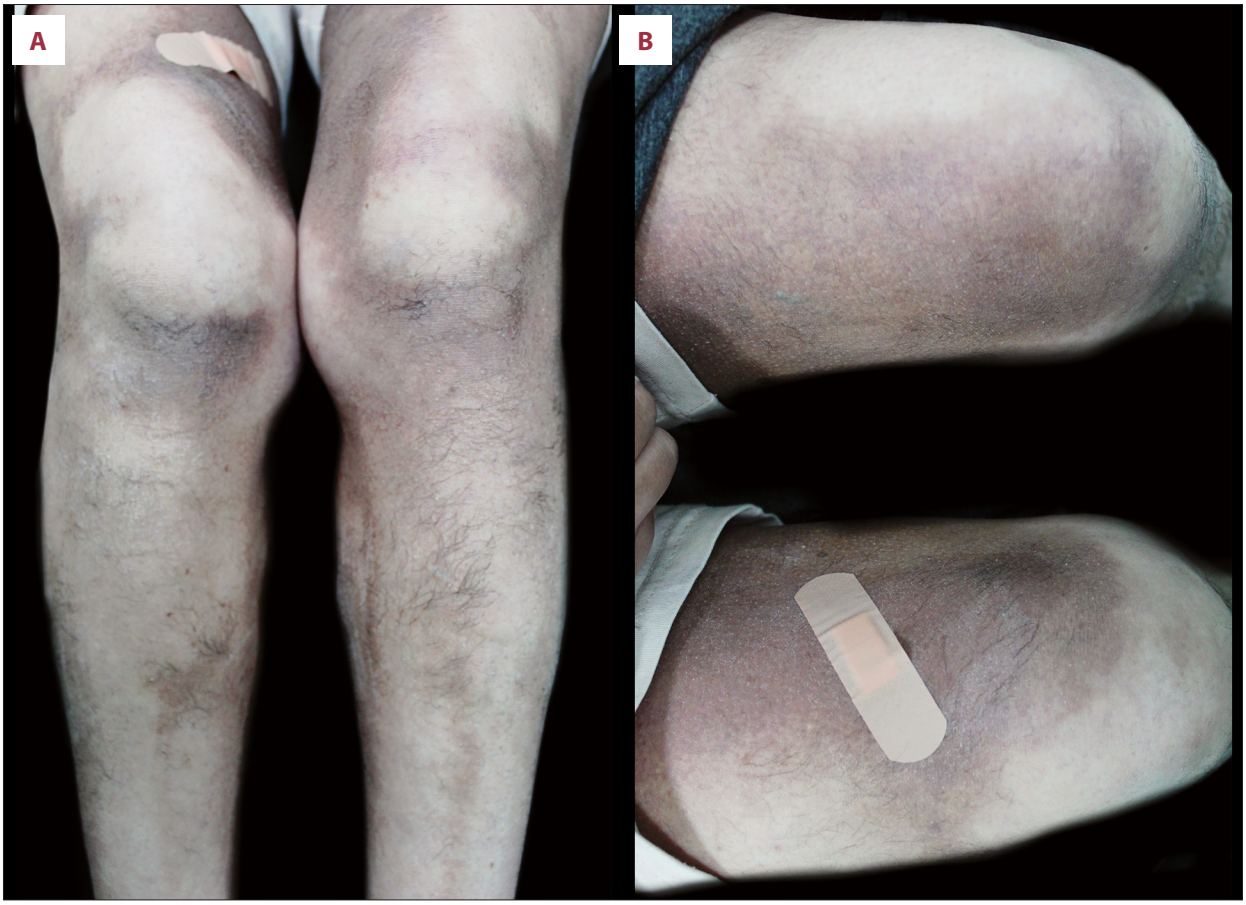

Figure 1. (**A**) Hyperpigmented-violaceous sclerotic plaques symmetrically involving the bilateral inner thighs, inner legs, and lower knees. (**B**) Close-up view of the sclerotic skin changes showing the hypertrichosis.

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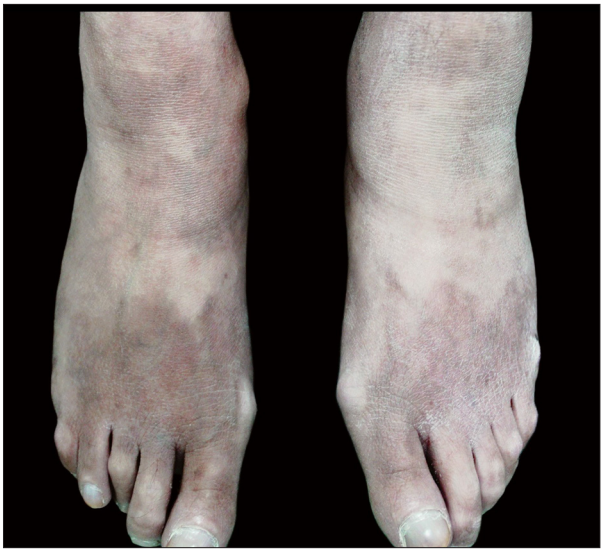

Figure 2. The pigmented sclerosis of the dorsal forefoot, along with the hallux valgus of the big toe.

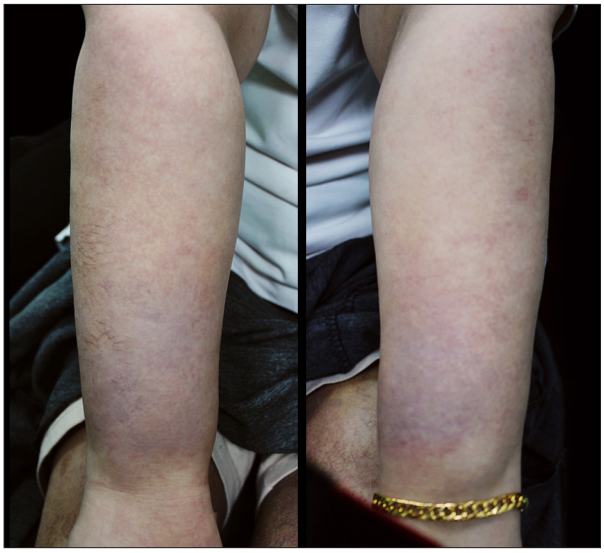

Figure 3. Erythematous to violaceous skin changes of the bilateral dorsal forearms with focal hypertrichosis.

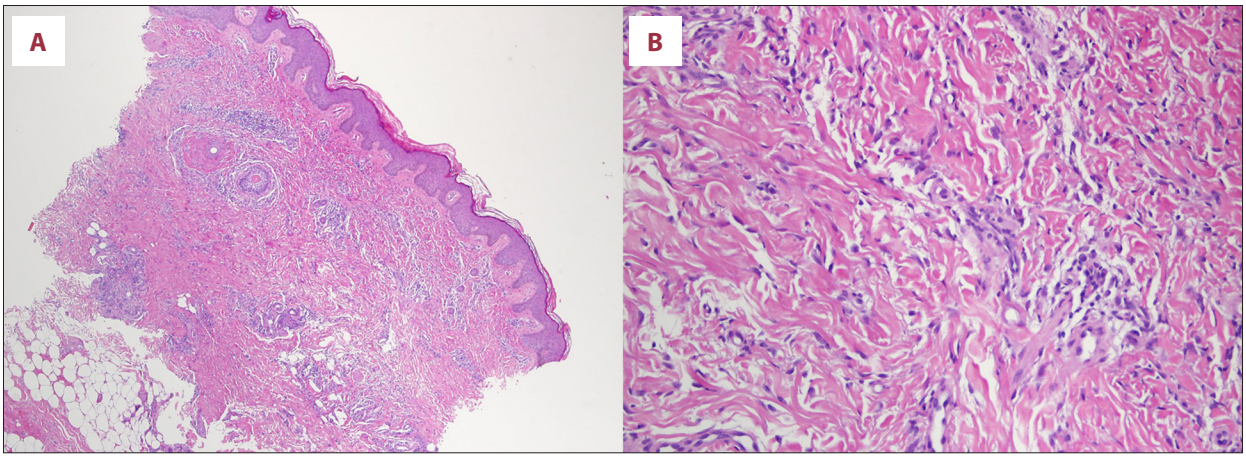

Figure 4. (**A**) 10× hematoxylin and eosin stained histopathologic slide showing the sclerotic dermis, thick collagen bundles extending to the deep subcutaneous fat, and the peri-vascular, peri-adnexal inflammatory infiltrate. (**B**) 40× hematoxylin and eosin stained slide showing the interstitial lymphoplasmacytic infiltrate along with an increased number of fibroblasts.

marrow biopsy, which showed anemia of chronic disease. She has a history of chronic joint pain as well, which was labelled by her rheumatologist as a non-defined autoimmune connective tissue disease.

Upon physical examination, the patient was short in stature, and cutaneous examination revealed symmetrical indurated hyperpigmented to violaceous plaques over the medial thighs, upper legs, lower back, volar wrists, and upper arms, associated with hypertrichosis. Hallux valgus of the big toes was clinically detected as well (**Figures 1-3**). By palpation, cervical lymphadenopathy was identified.

Skin punch biopsy of the indurated plaques showed moderate perivascular, peri-adnexeal, and interstitial lymphoplasmacytic infiltrate, increased number of fibroblasts, and superficial dermal melanophages. There was a focal extension of the dermal collagen into the underlying subcutaneous fat, which was otherwise unremarkable (**Figure 4**).

Laboratory test results showed a white blood cell count of 3.7×10^9/L, hemoglobin level of 10.4 g/dL, mean corpuscular volume of 75.2 fL, hematocrit of 33.4%, reticulocyte distribution width of 20.9%, platelet count of 319×10^9/L, erythrocyte sedimentation rate of 59 mm/h, glucose level of 10.66 mmol/L, and Hb A1C of 9.3%. Antinuclear antibody was positive homogenous at 1: 640; however, anti-dsDNA antibodies were negative. She had normal liver and renal profiles.

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Ultrasound of the abdomen was done looking for any signs of organomegaly; however, it showed no signs of splenic or hepatic enlargement.

Genetic analysis of the patient showed a homozygous frameshift pathogenic variant of the SLC29A3 gene, c.243del p.(Lys81Asnfs*20), confirming the diagnosis of histiocytosis-lymphadenopathy plus syndrome. We tried oral methotrexate to treat her cutaneous sclerotic lesion, but she failed to respond again.

She received a several months' course of imatinib mesylate in another outside facility, from the same physician who treated her sister. The imatinib was initially used to control her sister's robust histiocytic proliferative presentation; however, no notable changes in our patient's medical/cutaneous symptoms were appreciated.

Discussion

H syndrome is an autosomal recessive disorder of histiocytosis. It has a wide range of clinical manifestations depending on the organ affected. The name of the syndrome "H" was suggested because of the first description of its clinical findings: hyperpigmentation, hypertrichosis, hyperglycemia, heart anomalies, hearing loss, low height, hypogonadism, and hepatosplenomegaly [1].

The syndrome starts to manifest during the first decade of life, as in our patient, with sensorineural hearing loss, delayed growth, and/or cardiac anomalies [8]. Later on, during the first to second decades of life, hyperpigmented sclerodermatous changes start to appear, mainly covering the middle and lower body parts [1,2,7]. Interestingly, although our patient's upper body parts, including the arms and chest, were uniquely involved, the pattern of the disease spread starting from the inner thighs and spreading upward was noticed in our case, as described earlier by El-Khateeb [9].

The rest of its clinical presentations can be classified into either histiocyte proliferative-related entities, extensive lymphadenopathy, and hepatosplenomegaly, or into impaired immune inflammatory reparative process, hearing loss, insulin-dependent diabetes, sclerotic skin changes, and flexural contractures. It is hypothesized that SLC29A3 mutation exhausts stem cell regenerative potential. Consequently, whenever an organ is exposed to an infectious or traumatic injury, impaired reparative process, coupled with the induced histiocyte proliferation into injured tissues, leads to organ fibrosis [10,11]. Infrequently reported, our patient developed hypothyroidism early in her life, which was similarly reported previously [12]. As in our patient, joint pain combined with an elevated erythrocyte sedimentation rate level and positive antinuclear antibody might confuse the diagnosis [2]. However, these findings were not enough to fulfil the clinical and immunologic criteria proposed for the diagnosis of systemic lupus erythematosus [13].

Although standard treatment is lacking, the latest discoveries of the gene mutation and the suggested pathophysiology of the disease can aid clinicians in avoiding unnecessary available immunosuppressive medications. For instance, several immune suppressive medications (anti-tumor necrosis factor, anti-interleukin 1, cyclosporine, azathioprine) have been tried with limited to no success [14,15]. The anti-sclerotic immune-suppressive medications mycophenolate mofetil [16], methotrexate [14], and tocilizumab (anti IL-6) [14], on the other hand, showed promising results in the treatment of sclerotic skin changes, arthritis, and short stature, respectively. In parallel with the previous results, we had tried methotrexate therapy for several months; however, it gave only a minimal response regarding the joint pain but did not improve the sclerotic skin changes. Imatinib, an inhibitor of the profibrotic mediators, platelet-derived growth factor and transforming growth factor beta, was suggested to be used for treating scleroderma, as it was hypothetically assumed that it might prevent the progression of the fibrosis and regress the established fibrotic changes [17,18]. However, our patient also failed to respond to imatinib.

Conclusions

Fifteen years after the first description of H syndrome, a growing disclosure of its characteristics has been re-presented. Although the understanding of its pathogenesis evolution is mainly delivered from the reported cases and latest genetic discoveries, disease management is still challenging. Knowing the early life presentation and variable clinical symptoms of the disease is crucial in early intervention and further prevention of the non-reversible changes. Moreover, avoiding unnecessary immunosuppressive medication use is warranted in certain circumstances.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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