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H Syndrome: A Case Series of 3 Patients was First Described in Syria and a Literature Review

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Introduction

Monogenic auto-inflammatory diseases are a group of hereditary disorders characterized by a clinical and biological inflammatory syndrome without evidence of autoimmunity. The mutated proteins are involved in the altered regulation of inflammation (1). The H syndrome has been recently described as a rare monogenic auto-inflammatory autosomal recessive histiocytosis, with a prevalence of less than 1 in 1,000,000. It is characterized by typical cutaneous findings and associated systemic manifestations(2).It is caused by mutations in the solute carrier family 29 (SLC29A3) gene, which encodes the human equilibrative nucleoside transporter-3(hENT3), a protein found in endosomes, lysosomes, and mitochondria(3).It was first described by Molho-Pessach et al in 2008, also naming it H syndrome considering the fact most of the clinical features start with the letter "H" (4) and the first described cases were from Arab descendant (7) .Thereafter, about 100 patients of H syndrome have been described worldwide(5). H syndrome is now considered to include pigmented hypertrichosis with insulin dependent diabetes mellitus syndrome (PHID), Faisalabad histiocytosis (FHC), and familial sinus histiocytosis with massive lymphadenopathy (FSHML).(2). Symmetrical cutaneous hyperpigmentation involving inner thighs accompanied by hypertrichosis and sclerodermatous induration are the most common features observed and considered hallmark of the disease.

Case presentation

Patient 1: A 15-year-old male presented with asymptomatic bilateral hyper-pigmented patches on the lower limbs, his medical history reveals congenital glaucoma and delayed puberty. On examination: short stature (152cm), stiffness dark brown well demarcated patches on lower limbs, exophthalmos and dilated scleral vessels, flexion contractures in some fingers. Lab tests were within normal except (HGB: 10g/dl, AST: 150U/L, ALT: 187U/L, testosterone: 100ng/dl, HbA1c: 9.3%).

Patient 2: A 15-year-old female presented with bilateral hyper-pigmented plaques on thighs and shines, her medical history reveals bilateral hearing loss, amenorrhea, tingling in the fingertips, excessive thirst and urination and the familial history shows bilateral hearing loss diagnosed in her brother. On examination: bilateral pigmented well demarcated patches on thighs and shins, exophthalmos, bilateral inguinal lymphadenopathy and erythema. Lab tests were within normal except (glucose: 458mg/dl, Esr: 60mm/hr, HbA1c: 17%, LH/FSH: 17). Axillary echography shows multiple masses exceed 1cm in diameter, inguinal echography shows bilateral oedema in subcutaneous tissue.

Patient 3: A 16-year-old female presented with hyper-pigmented patches on thighs and genitalia, her medical history reveals moderate hearing loss, heart disorders, primary amenorrhea, IDDM. On examination: short stature (130cm), stiffness hyperpigmented well demarcated patches on genitalia and thighs, spleenomegaly, flexion contractures in two fingers and 4 toes. Lab tests were within normal except: (HGB: 7.4g/dl, MCV: 70fl, glucose: 320mg/dl, ESR: 123mm/hr, GH: 0.05ng/ml). peripheral blood smear showed microcytic

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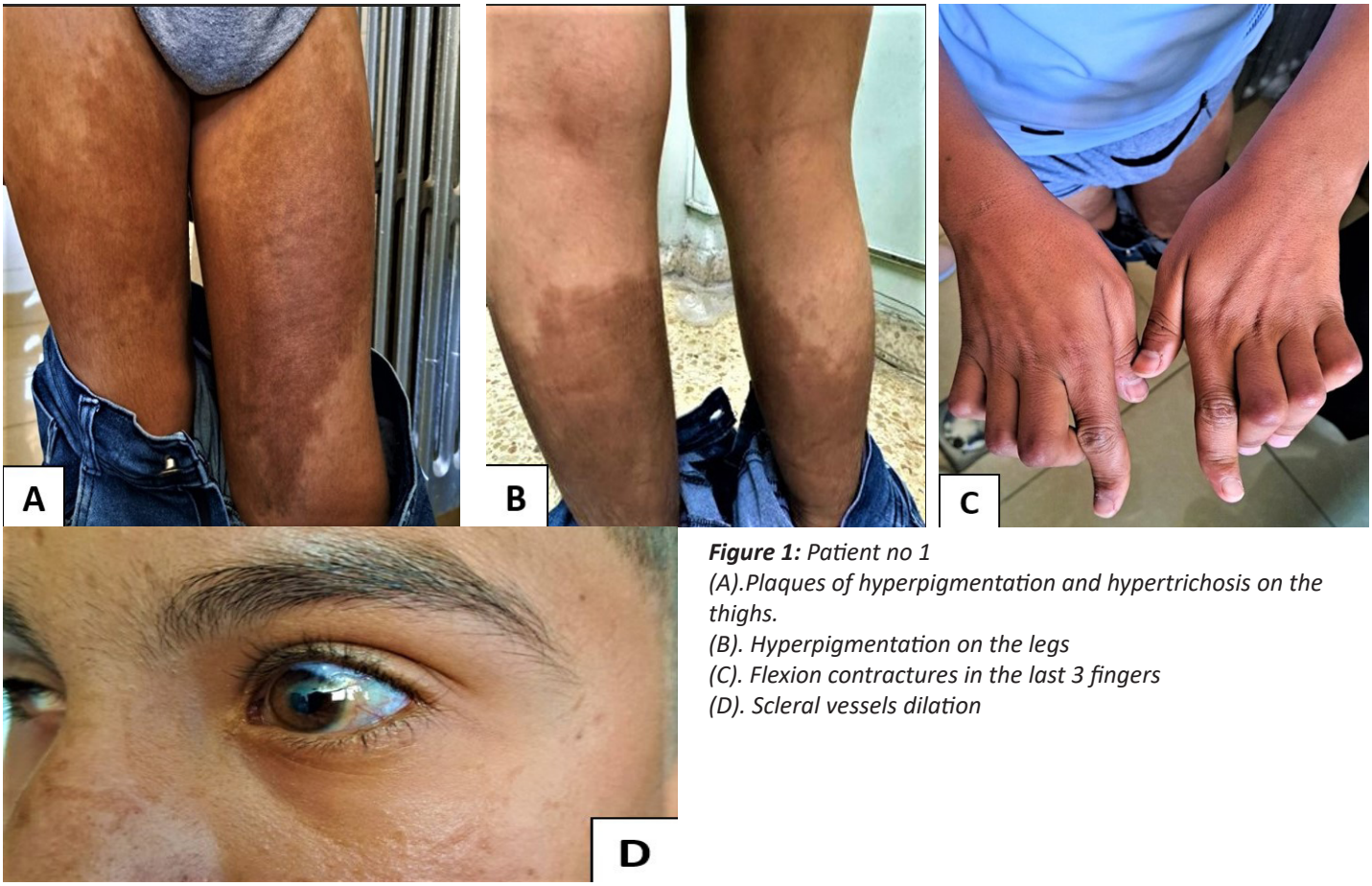

Figure 1: *Patient no 1*
(A).Plaques of hyperpigmentation and hypertrichosis on the thighs.
(B). Hyperpigmentation on the legs
(C). Flexion contractures in the last 3 fingers
(D). Scleral vessels dilation

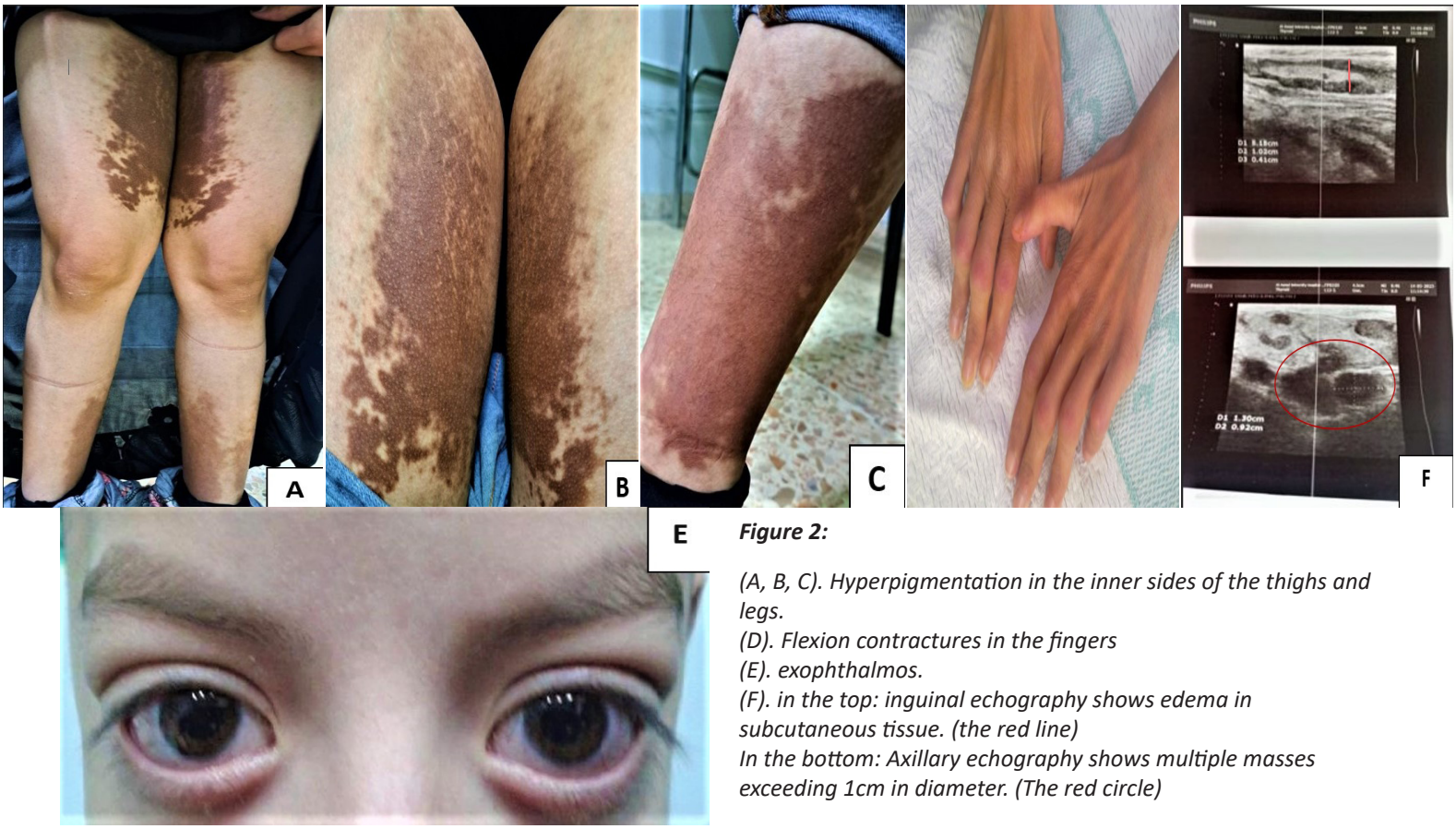

Figure 2:

(A, B, C). Hyperpigmentation in the inner sides of the thighs and legs.
(D). Flexion contractures in the fingers
(E). exophthalmos.
(F). in the top: inguinal echography shows edema in subcutaneous tissue. (the red line)
In the bottom: Axillary echography shows multiple masses exceeding 1cm in diameter. (The red circle)

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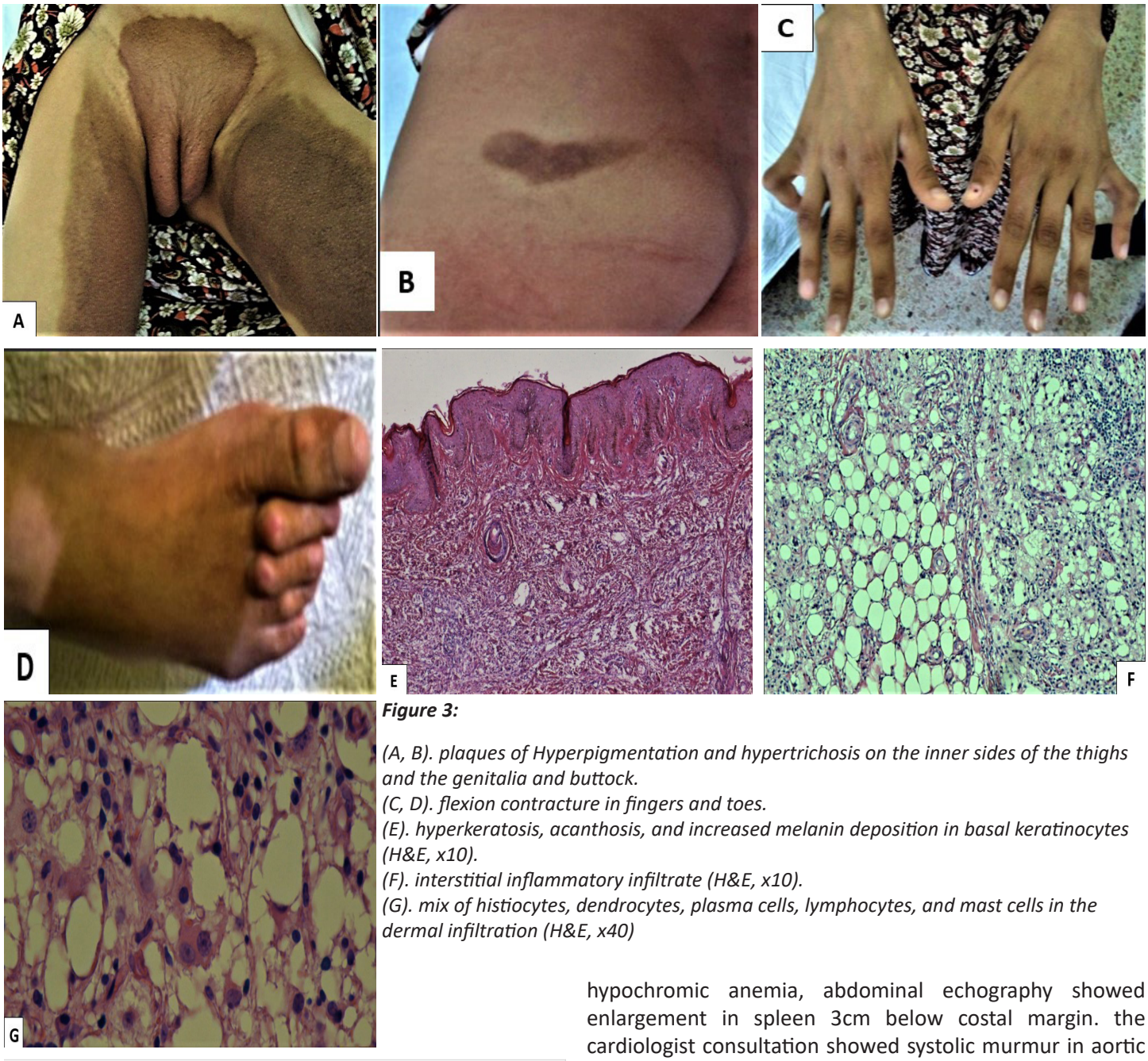
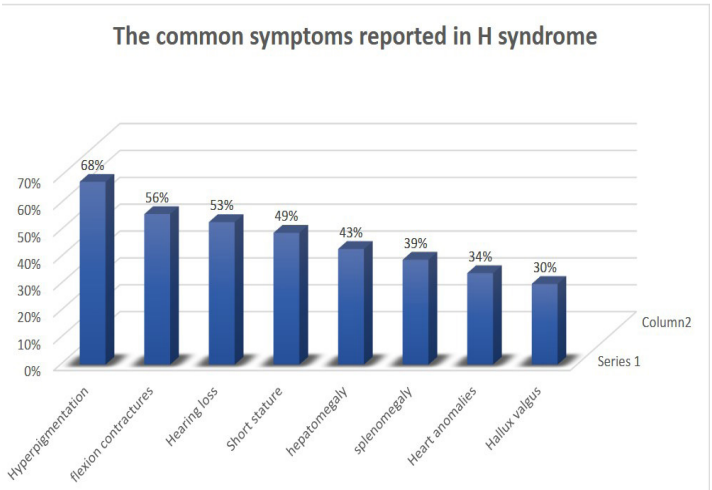


Figure 3:

(A, B). plaques of Hyperpigmentation and hypertrichosis on the inner sides of the thighs and the genitalia and buttock.
(C, D). flexion contracture in fingers and toes.
(E). hyperkeratosis, acanthosis, and increased melanin deposition in basal keratinocytes (H&E, x10).
(F). interstitial inflammatory infiltrate (H&E, x10).
(G). mix of histiocytes, dendrocytes, plasma cells, lymphocytes, and mast cells in the dermal infiltration (H&E, x40)



hypochromic anemia, abdominal echography showed enlargement in spleen 3cm below costal margin. the cardiologist consultation showed systolic murmur in aortic valve area, echocardiography showed: tricuspid and mitral regurgitation, secondary ASD measures 1.2cm.

Discussion

H syndrome, also known as Hermansky-Pudlak syndrome type 9 (HPS9), is a rare genetic disorder characterized by various symptoms. It is a multisystem disorder that affects different parts of the body, including the skin, eyes, and lungs. In the first cases reported progressive sclerodermatous thickening accompanied by hyperpigmentation of lower and middle body parts were the significant finding. chart (1)

The lesions start to appear mainly in the first or second decade of life (7). It is called H syndrome due to constellation of symptoms with "H": Hyperpigmentation, Hypertrichosis,

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Hepatosplenomeg aly, Hearing loss, Hypogonadism, Hyperglycemia, Hallux valgus, Histiocytosis, Heart anomaly, Hypertelorism, Hypothyroidism.

Other manifestations include: short stature, Flexion contractures, Sclerodermatous, Arthritis, Lymphadenopathy, Gynecomastia, Dilated scleral vessels, Micropenis, Genital masses, Exophthalmos, Varicose veins. skin biopsy of the pigmented lesions shows: Hyperkeratosis, acanthosis, increased melanin deposition in basal keratinocytes, Significant thickening of collagen bundles in upper and mid-dermis was seen along with perivascular infiltrate of histiocytes. Immunohistochemistry was positive for CD68, S100, CD1a and CD45 in dermal perivascular histiocytic infiltrate and for CD34+ in vessel endothelium and factor 13a+ dendrocytes. same findings were seen in biopsies from enlarged lymph nodes and from nasal mucosa biopsies. (6,8).

Diagnosis is Mainly by clinical and histopathological findings. Genetic testing mainly by WES (Whole Exome Sequencing) and sanger squencing for scientific purposes and screening in families.

H syndrome does not have any standard treatment for preventive and therapeutic approach toward its cutaneous and systemic presentations apart from hypertrichosis that could be almost permanently removed by laser. However, the latest findings suggest that there is possibility of prevention of short stature or other cutaneous and systemic complications in this syndrome with earlier diagnosis and treatment.

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