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AN UNUSUAL SYNDROMIC PRESENTATION IN DIABETES: HISTIOCYTOSIS-LYMPHADENOPATHY PLUS SYNDROME

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ABSTRACT

Introduction: Histiocytosis-lymphadenopathy plus syndrome is a rare autosomal recessive multisystemic disorder caused by mutations in the *SLC29A3* gene, which encodes the nucleoside transporter hENT3. This mutation has been linked to a group of syndromic histiocytoses including H-syndrome, pigmented hypertrichosis with insulin-dependent diabetes, Faisalabad histiocytosis and familial Rosai-Dorfman disease.

Case description: We report the case of an 18-year-old woman from an Arab country with no parental consanguinity who presented to our department with uncontrolled diabetes, repeated severe hypoglycaemic episodes, short stature and delayed puberty. Her history included exocrine pancreatic insufficiency, marked skin hyperpigmentation with thickening of the lower limbs, skeletal deformities, chronic anaemia, impacted teeth and a constellation of findings strongly evocative of H-syndrome. In addition, she presented with multiple deep lymphadenopathies.

Discussion: This case reflects the variable expression of H-syndrome. We report, for the first time, dental inclusion as a possible additional feature of this syndrome. The patient presented with a severe systemic form involving multiple organs, including pancreatic insufficiency, diabetes with persistent glycaemic instability despite multiple daily insulin injections and close monitoring, delayed puberty requiring initiation of transdermal oestradiol therapy, and dermatological manifestations poorly responsive to topical treatments. These findings underscore both the heterogeneity of clinical presentation and the challenges in managing H-syndrome.

Conclusion: With fewer than 100 cases described worldwide, histiocytosis-lymphadenopathy plus syndrome remains vastly underdiagnosed. This case highlights the importance of recognising its characteristic clinical features and aims to raise awareness among clinicians, encouraging them to consider uncommon diagnoses when faced with unusual combinations of dermatological, endocrine and skeletal signs.

KEYWORDS

Histiocytosis-lymphadenopathy plus syndrome, H-syndrome, SLC29A3 gene, human equilibrative nucleoside transporter (hENT3), deformities, skin hyperpigmentation, diabetes mellitus

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LEARNING POINTS

- Histiocytosis-lymphadenopathy plus syndrome is a rare autosomal recessive multisystem disorder caused by *SLC29A3* mutations.
- Diagnosis relies on clinical, histopathological and genetic findings, and should be considered in patients with atypical combinations of cutaneous, endocrine and skeletal features.
- Multisystem involvement is associated with increased morbidity.

INTRODUCTION

Histiocytosis-lymphadenopathy plus syndrome is a rare autosomal recessive condition caused by mutations in the *SLC29A3* gene, which encodes the human equilibrative nucleoside transporter. This syndrome comprises several disorders that are characterised by abnormal histiocytic proliferation and are thought to be separate entities, including H-syndrome, Faisalabad histiocytosis, pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome, and sinus-histiocytosis with massive lymphadenopathy[1]

The diagnosis is often challenging and is suspected after a comprehensive history, physical examination and detailed family history review, with confirmation through genetic testing for *SLC29A3* mutations[2].

We present the case of an 18-year-old female diagnosed with histiocytosis-lymphadenopathy plus syndrome from a non-consanguineous family, aiming to emphasise the numerous clinical features of this rare condition and to enhance physicians' awareness in diagnosing this syndrome.

CASE DESCRIPTION

An 18-yearold Arabic female was admitted to our endocrinology, diabetology and nutrition department for uncontrolled diabetes, short stature and delayed puberty. She is the third-born of seven siblings from a non-consanguineous marriage.

At the age of 7 years, she presented progressive weight loss associated with a polydipsia-polyuria syndrome, prompting medical consultation. She was subsequently diagnosed with insulin-dependent diabetes mellitus and exocrine pancreatic insufficiency. At the age of 12 years, she developed progressive hyperpigmentation and cutaneous thickening. At the age of 15 years, a molecular analysis by next-generation sequencing identified a novel homozygous mutation in the SLC29A3 gene, which is found in histiocytosis-lymphadenopathy plus syndrome.

The family history showed that two of her brothers exhibited similar features. The parents and four other siblings were healthy and showed no signs of the features described here *(Fig. 1)*.

Physical examination revealed a short stature with a height of 139 cm (−4.3 SD and 4 SD below the midparental height), a weight of 38 kg (−2.7 SD). She has an infantile face, fine hair, dental impactions and abdominal adiposity. The dermatological examination showed indurated-hyperpigmented plaques involving the inner thighs and lower legs. Musculoskeletal examination revealed ankylosing deformities of the proximal interphalangeal joints in both the hands and feet, cubitus valgus and bilateral hallux valgus *(Fig. 2)*. A hepatomegaly was also observed. The sexual maturity rating was Tanner Stage 1 for breast development and axillary hair, Tanner Stage 2 for pubic hair, and she had primary amenorrhoea.

The blood tests revealed hypochromic microcytic anaemia; the assessment of vitamin and iron status revealed no abnormalities. The lipid panel revealed hypertriglyceridemia, for which she received lifestyle and dietary measures associated with fenofibrate treatment. The renal, liver and thyroid function tests were normal. (A summary of the biological findings is presented in *Table 1*.)

The fasting C-peptide level was low at 0.03 ng/ml with a concomitant glycaemia level of 1.03 g/l. Faecal-elastase level was at 15 µg/g (normal range >200 µg/g), indicating severe pancreatic insufficiency.

The gonadal assessment revealed hypogonadotropic hypogonadism. During the follow-up she exhibited pubertal stagnation (Breast Tanner Stage 2) and was started on

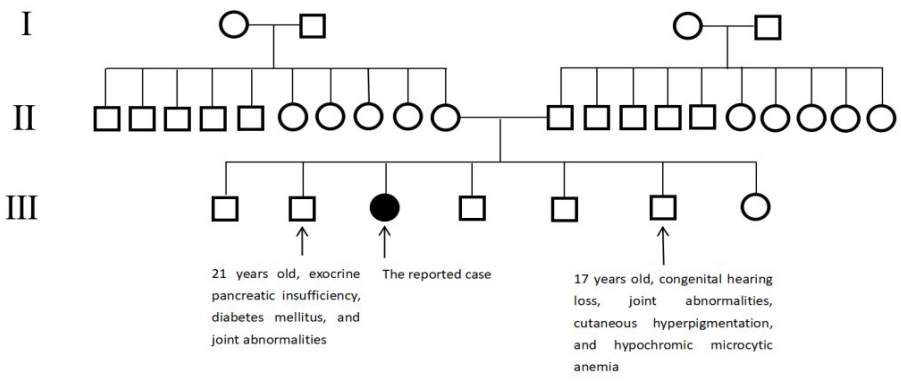


Figure 1. *Patient's family tree.*

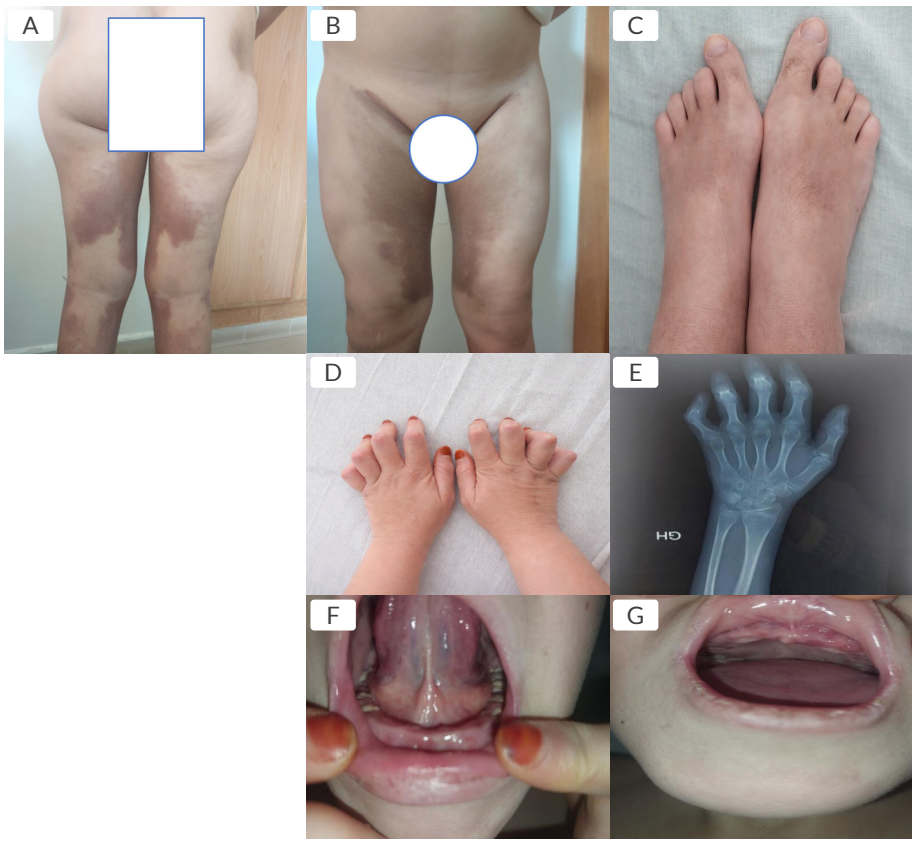


Figure 2. The dysmorphic syndrome symptoms observed in our patient. A, B, C) Symmetrical hyperpigmented and indurated patches involving the inner thighs, calves and feet, with bilateral hallux valgus. D, E) Ankylosing deformities of the proximal interphalangeal joints in both hands. F, G) Dental inclusion.

hormone replacement therapy. The echocardiography evaluation did not reveal any cardiac abnormalities, along with cardiomegaly on chest X-ray.

A mechanical type back pain was reported in our patient. A full spine X-ray revealed diffuse vertebral compression, with an osteoporosis among the bone densitometry. The bone age was 17 years for a chronological age of 18 years, and a Risser stage of 5. The hypothalamus-pituitary magnetic resonance imaging (MRI) was normal. An abdominal-pelvic computed tomography (CT) scan showed bilateral hypertrophy and infiltration of the adrenal glands. Multiple bilateral retroperitoneal, iliac and inguinal lymphadenopathies were noted, along with significant infiltration of the abdominal posterior parietal subcutaneous soft tissues, perineal, inguinal and proximal crural regions. A pancreatic MRI was performed, revealing pancreatic hypotrophy with loss of normal T1 signal *(Fig. 3)*.

DISCUSSION

Histiocytosis-lymphadenopathy plus syndrome is a worldwide, extremely rare genetic disorder that is becoming more recognised in recent years. It is characterised by multisystem involvement and phenotypic overlap with several other syndromic entities. Its prevalence remains unclear, with only a few hundred reported cases since it was first described in 2008 – approximately 100 to 120 documented cases in the worldwide literature[1,3]. The estimated incidence is fewer than 1 case per 1,000,000 individuals[4]. This condition has been reported in patients from various ethnic backgrounds, including those from the Middle-East, Europe, Asia and[3-7].

Given its autosomal recessive mode of inheritance, it is expected to be more prevalent in populations with high rates of consanguinity. However, in this case, our patient was born to non-consanguineous parents.

Similar to the previously reported cases in the literature, our patient exhibited characteristic manifestations of H-syndrome including hyperpigmentation of the lower limbs, flexion contractures of the fingers and short stature – features frequently considered pathognomonic of the condition[3]. In contrast, she did not present any hypertrichosis or sensorineural hearing loss. Remarkably, she exhibited dental inclusion – a finding which, to the best of our knowledge, represents the first reported feature in this syndrome.

The prognosis of H-syndrome is highly variable depending on multiple factors, including the severity and extent



Figure 3. Abdominal MRI demonstrating pancreatic hypotrophy (arrow).

Parameter	Value	Range
Haemoglobin (g/dl)	9.9	12–16
Mean corpuscular volume (fl)	76	80–98
Mean corpuscular haemoglobin concentration (%)	30.6	32–36
Ferritin level (ng/ml)	148	20–200
Vitamin B9 level (ng/ml)	9.9	>9
Vitamin B12 level (pg/ml)	596	187–883
Vitamin D level (ng/ml)	11.7	30–70
Calcaemia (mg/l)	88	84–102
Phosphoraemia (mg/l)	49	23–47
Albuminaemia (g/l)	28	35–50
Aspartate aminotransferase (UI/l)	16	5–34
Alanine aminotransferase (UI/l)	10	0–55
Total bilirubin (g/l)	2.7	2–12
Direct bilirubin (g/l)	1	0–5
Alkaline phosphatase (UI/l)	186	<500
Gamma-glutamyl transferase (UI/l)	18	9–36
Creatininemia (g/l)	5.7	5.7–11.1
Cholesterol (g/l)	1.25	<2
High-density lipoprotein (g/l)	0.12	>0.6
Low-density lipoprotein (g/l)	0.48	_
Triglycerides (g/l)	3.12	<1.5
Cortisol level at 8:00 AM (µg/dl)	12.8	_
Ultra-sensitive thyroid stimulating hormone (mUI/ml)	1.3	0.35–4.94
Follicle-stimulating hormone (mUI/ml)	2.74	_
Luteinizing hormone (mUI/ml)	0.51	_
Oestradiol (pg/ml)	26	_
Prolactin (ng/ml)	10	5–26

Table 1. Biological findings of the patient.

of clinical manifestations, the presence of systemic complications, and the timing of diagnosis and therapeutic intervention. Patients with multisystem involvement generally have a less favourable outcome[2]. In this case, our patient exhibited multisystem manifestations conferring an adverse prognosis.

The therapeutic approach remains largely symptomatic and individualised, targeting specific clinical manifestations to improve patient outcomes and quality of life. The laser therapy for hypertrichosis, the recombinant human growth hormone administration during childhood, the sex hormone replacement therapy in cases of hypogonadism and the use of hearing aids for sensorineural deficits are some of the major interventions. Although there is growing evidence for an underlying autoinflammatory pathogenesis, there is currently a lack of consensus on the treatment of the primary pathophysiology of this disorder.

Various reported pharmaceutical agents including corticosteroids, mycophenolate, tocilizumab, methotrexate, cyclosporine, cyclophosphamide, 6-mercaptopurine and adalimumab, have been employed with variable and often unpredictable efficacy[8-11]. However, a curative or consistently effective therapeutic regimen remains elusive, demonstrating the need for further research into the disease's molecular foundation and potential targeted therapies.

In this case, the patient was started on a basal–bolus insulin regimen to manage diabetes, which was marked by a significant glycaemic instability with fluctuating HbA1c levels between 8% and 12%, necessitating a close follow-up with regular dose adjustments. Regarding the pancreatic insufficiency, she was placed on pancreatic enzyme replacement therapy; however, due to limited resources she was unable to take it regularly, which further complicated the management of diabetes and led to multiple recurrent episodes of severe hypoglycaemia. For pubertal development, hormone replacement therapy was initiated, beginning with transdermal oestradiol at a dose of 0.25 mg/day with gradual adjustment to ensure proper breast development with further transition to combined oestrogen–progestin replacement.

To date, and to the best of our knowledge, among the 131 cases of histiocytosis-lymphadenopathy plus syndrome reported in the literature, 51 have been associated with diabetes mellitus, many of which exhibit clinical features similar to those observed in our patient[11-14] *(Table 2)*.

This is another case from an Arab country, adding to the limited number of reports on this rare condition. Most published cases have been reported in the context of parental consanguinity, supporting its autosomal recessive inheritance; however, our patient was born to non-consanguineous parents, suggesting that the syndrome may occur outside the classical genetic background. Our reported dental inclusion as a previously undescribed clinical feature expands the phenotypic spectrum of the disorder. The patient presented with a severe systemic form involving multiple organs, pancreatic insufficiency, diabetes with persistent glycaemic instability despite multiple daily insulin injections and close monitoring, delayed puberty requiring initiation of transdermal oestradiol therapy, and dermatological manifestations poorly responsive to topical treatments. These findings underscore both the heterogeneity of clinical presentation and the challenges of management.

	Our case	Patient 1[11]	Patient 2[12]	Patient 3[13]	Patient 4[14]
Genotype	Homozygous	Homozygous	Homozygous	Heterozygous	Homozygous
Origin	Moroccan	Indian	Egyptian	Italian	Moroccan
Gender	Female	Female	Female	Female	Female
Consanguinity	Unrelated parents	Consanguineous marriage	Consanguineous marriage	Unrelated parents	-
Age at the first manifestation	7 years	1 year	6 years	1 year	17 years
Age at diagnosis	15 years	5 years 9 months	8 years	21 years	37 years
Features	– Diabetes mellitus – Exocrine pancreatic insufficiency – Symmetrical skin hyperpigmentation + induration – Growth retardation – Toes and fingers, ankylosing deformities – Hypochromic microcytic anaemia – Hypogonadotropic hypogonadism – Dental impactions – Cardiomegaly – Hepatomegaly – Bilateral hypertrophy and infiltration of the adrenal glands – Bilateral retroperitoneal, iliac and inguinal lymphadenopathies	– Antibody negative diabetes mellitus since the age of 1 year – Bilateral sensorineural hearing loss – Hepatosplenomegaly – Short stature – Mitral regurgitation – Megaloblastic anaemia	– Diabetes mellitus – Hyperpigmentation + hypertrichosis of both thighs – Short stature – Left-sided sensorineural hearing loss – Bilateral exophthalmos – Absent left pectoralis major muscle	– Diabetes mellitus – Pancreatic insufficiency, toes and fingers deformities + clinodactyly with diffuse arthralgias and muscular pain with walking difficulties – Bilateral sensorineural hearing loss at the age of 6 years – Growth retardation – Frequent episodes of lymphadenopathy – Hepatosplenomegaly – Biological inflammation	– Diabetes mellitus – Sensorineural hearing loss – Symmetrical hyperpigmentation+ thickening of the legs – Skeletal deformities – Splenomegaly, bilateral perirenal, retroperitoneal and diffuse abdominal infiltration with right pleural effusion. – Periaortic fatty infiltration associated with posterior – mediastinal adenomegaly, paracardiac tumour lesions and pericardial effusion.
Treatment	– Dermatological topical treatment – Transdermal 17-β-oestradiol replacement therapy – Pancreatic enzyme substitution – Basal-bolus insulin regimen – Functional rehabilitation	Mycophenolate mofetil + supportive treatment	Topical steroid	Baricitinib + hydroxychloroquine	Tocilizumab (8 mg/kg) + corticosteroid
Outcomes	– Lack of efficacy on dermatological features – Ongoing monitoring of puberty – Persistent glycemic instability despite multiple therapeutic adjustments – Ineffective on articular deformities		Minimal improvement observed after 2 years' follow-up	Rapid and persistent normalisation of inflammatory markers, reduced pain and improved functional capacity	– After 6 months of treatment: regression of lymphadenopathy, splenomegaly, perirenal infiltration – Partial improvement of cutaneous manifestations – Ineffective on articular deformities, diabetes or hearing loss

Table 2. A summary of similar reported cases.

The wide variability in how this syndrome appears from one patient to another often makes it difficult to recognise. In regions where consanguinity is common, such as in our population, clinicians need to be attentive to the distinctive skin signs, such as hyperpigmentation and induration, that often serve as early clues. Recognising these signs can lead to earlier screening for systemic involvement, timely management and more informed genetic counselling for families.

CONCLUSION

Histiocytosis-lymphadenopathy plus syndrome is rarely reported internationally or discussed in medical literature. Its phenotypical heterogeneity, and its complex overlap with other medical conditions make it one of the very challenging cases to diagnose during practice. Early diagnosis and management are linked to favourable outcomes and prognosis. To date, its management is based on experimental approaches, with corticosteroids currently

constituting the predominant management option. We add a new case to the literature to increase the awareness regarding this syndrome, highlighting dental inclusion as a novel feature that is the first time, to our knowledge, to be reported in this syndrome. Despite being a single case report, this observation may carry substantial implications for the diagnosis of other individuals affected by this rare and neglected condition.

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