A Rare Autoimmune Disease Detected in the Differential Diagnosis of Immunodeficiency: Histiocytosis-lymphadenopathy Plus Syndrome

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ABSTRACT

Mutations in the SLC29A3 gene cause histiocytosis-lymphadenopathy plus (H) syndrome, a rare autosomal recessive genetic condition that affects numerous systems. We present a 7-year-old Syrian patient with pericardial effusion whose acute phase reactants did not decrease despite treatment. In order to emphasize the variety and raise awareness of H syndrome in the hopes of achieving an early diagnosis and appropriate treatment, molecular investigation of SLC29A3-related disorders is crucial. H syndrome is an uncommon genetic condition with a broad spectrum of phenotypes. Therefore, early genetic testing is essential for the accurate diagnosis of patients. Doctors should be aware of this condition and its symptoms and consider autoimmune diseases as a possible alternative diagnosis in patients with suspected immunodeficiency.

Keywords: Autoimmunity; Histiocytosis; Lymphadenopathy

INTRODUCTION

Histiocytosis-lymphadenopathy plus syndrome (H syndrome; MIM:602782) is an autosomal recessive condition caused by mutations in the SLC29A3 gene, which codes for the human equilibrative nucleoside transporter (hENT3). About 100 patients, some of Arab origin, have been reported in the literature with an estimated incidence of 1/1,000,000.¹ The syndrome is named after its common clinical features, such as hypertrichosis, hepatosplenomegaly, hyperpigmentation, hearing loss, cardiac abnormalities, hypogonadism, and hyperglycemia.² Other manifestations include microcytic anemia, lymphadenopathy, hallux valgus, camptodactyly, and flexion contractures of the proximal interphalangeal joints. A distinctive sign of H syndrome is the presence of skin lesions on the lower limbs, especially on the medial sides of the thighs. Histopathological findings of these lesions include epidermal hyperplasia with increased basal pigmentation, dermal infiltrates of histiocytes, lymphocytes, and plasma cells with hemosiderin deposits and calcifications.³,⁴ Rosai-Dorfman disease, characterized by infiltrating CD68⁺, S100⁺, and CD1a histiocytes, is comparable to histiocytosis if it is present.⁴

CASE PRESENTATION

A 7-year-old Syrian female patient with consanguineous parents (first cousins) was referred to us in Turkey after pericardial effusion was detected in echocardiography after 20 days of follow-up in an external center in Syria. She had presented with...
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malnutrition, weakness, and weight loss. Her general condition was moderate, and her height and weight were below the 3rd percentile for her age. She had cervical lymphadenopathies measuring at 2 to 5 cm, and submandibular scarring, as well as flexion contractures of the fingers (Figure 1A). She did not have hepatosplenomegaly.

The patient had no history of frequent infections, hospitalization due to infection, recurrent otitis media, fungal infections in the mouth or nails, recurrent dermatitis, and recurrent diarrhea. She had been operated on for submandibular lymphadenopathy in Syria 1 year ago, and the biopsy results showed chronic inflammation.

Pericardiocentesis was performed, and 120 mL of serous exudative pericardial fluid was drained. The patient was evaluated for tuberculosis, but no pathological findings were detected. Laboratory results showed microcytic hypochromic anemia, lymphopenia, elevated C-reactive protein, and elevated prohormone B-type natriuretic peptide (NT-proBNP). Table 1 summarizes the patient’s laboratory data.

The patient’s immunoglobulin G level was elevated, and lymphocyte subgroups were within the normal range for her age. Based on the lab findings and her syndromic facial appearance (Figure 1B), a genetic examination was sent for immunodeficiency and possible syndromes.

Table 1. The results of the laboratory tests of our patient

<table>
<thead>
<tr>
<th>Lab data</th>
<th>Normal range</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (/mm³)</td>
<td>4000–10,000</td>
<td>6300</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1500–6800</td>
<td>1060</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1500–8000</td>
<td>4310</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>11.4–15.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Platelets (/mm³)</td>
<td>150,000–400,000</td>
<td>564,000</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0–5</td>
<td>89</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>0–15</td>
<td>120</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>&lt;125</td>
<td>7273</td>
</tr>
<tr>
<td>IgA (mg/dL)</td>
<td>70–312</td>
<td>490</td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>600–1500</td>
<td>1980</td>
</tr>
<tr>
<td>IgM (mg/dL)</td>
<td>56–352</td>
<td>110</td>
</tr>
<tr>
<td>IgE (IU/mL)</td>
<td></td>
<td>217</td>
</tr>
<tr>
<td>CD19^+ (%)*</td>
<td>10–31</td>
<td>15</td>
</tr>
<tr>
<td>CD3^+ (%)*</td>
<td>55–78</td>
<td>64</td>
</tr>
<tr>
<td>CD3^+CD4^+ (%)*</td>
<td>27–53</td>
<td>37</td>
</tr>
<tr>
<td>CD3^+CD8^+ (%)*</td>
<td>19–34</td>
<td>23</td>
</tr>
<tr>
<td>CD16^+CD56^+ (%)*</td>
<td>4–26</td>
<td>24</td>
</tr>
</tbody>
</table>

Hb: hemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NT-proBNP: prohormone B-type natriuretic peptide; Ig: immunoglobulin; IU: international units; * percentage of lymphocytes.
The patient’s condition improved, and the pericardial effusion resolved after long-term treatment with broad-spectrum antibiotics. However, the patient’s acute phase reactants remained elevated. Rheumatological investigation showed normal C3 and C4 levels and negative results for anti-double-stranded DNA, antinuclear antibody, and genetic mutations for familial Mediterranean fever.

Whole exome sequencing revealed a homozygous mutation in SLC29A3: c.1157G>A p.(Arg386Gln), resulting in an amino acid substitution of glutamine for arginine at position 386 of hENT3. This mutation has previously been described as pathological in another Syrian patient.6

DISCUSSION

Molho-Pessach et al. were the first to describe the rare autosomal recessive condition known as H syndrome in 2008.3 Biallelic mutations in the SLC29A3 gene on chromosome 10q22 are the cause of the syndrome. SLC29A3 encodes hENT3, a transporter involved in the transport of nucleosides and nucleotide synthesis.7,8

Until 2023, different mutations were identified in SLC29A3, including missense, nonsense, and deletion mutations.5,9 We detected a mutation in a patient with lymphadenopathy, growth retardation, lymphopenia, and pericardial effusion.

The pathognomonic feature of the syndrome is skin hyperpigmentation with sclerodermatous thickening and hypertrichosis, which primarily affects the lower extremities. Symptoms usually appear in the first or second decade of life.5 Our patient had flexion contractures in the fingers and sclerodermatous thickening but no skin hyperpigmentation. Additionally, she had arthralgia, short stature, sensorineural hearing loss, lymphadenopathy, and high inflammatory marker levels.

H syndrome has a slow and progressive course, which can lead to an erroneous or delayed diagnosis.3 Therefore, findings that are not present in our patient may develop over time and should be evaluated at regular intervals.

H syndrome can cause various cardiac abnormalities, such as mild pulmonary stenosis, pericardial effusion, pulmonary hypertension, ductus arteriosus with right-to-left shunt, atrial and ventricular septal defects, mitral valve prolapse, cardiomegaly, and myocardial hypertrophy.2,3,10 These cardiac problems may result from the impaired nucleoside transport activity of the mutant hENT3 protein in the heart, which may affect normal cardiac functions and morphogenesis.11 Our patient was also referred to us for the investigation and treatment of pericardial effusion and was also consulted with us in terms of immunodeficiency due to lymphopenia.

In conclusion, H syndrome is an uncommon genetic condition with a broad spectrum of phenotypes. Therefore, early genetic testing is essential for the accurate diagnosis of patients. Doctors should be aware of this condition and its symptoms and consider autoimmune diseases as a possible alternative diagnosis.
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in patients with suspected immunodeficiency. Autoimmune diseases can cause inflammation that mimics the signs of infection.

STATEMENT OF ETHICS

Written informed consent for publication of the clinical details was obtained from the patient’s parents.

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This research did not receive any specific grant or fellowship from any funding agency. Written informed consent to publication has been obtained from the parents.

CONFLICT OF INTEREST

The authors declare no conflicts of interest concerning the research, authorship, or publication of this article.

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