OMCR

Oxford Medical Case Reports, 2020;11,415–418

doi: 10.1093/omcr/omaa106
Case Report

CASE REPORT

Hyper IgE syndrome (Job syndrome) in Syria: a case report

Rama Awad[1] and Ameer Kakaje[2,*,†]

[1]Department of Endocrinology, Al Mouwasat University Hospital, Damascus University, Damascus, Syria, [2]Damascus University, Damascus, Syria.

*Correspondence address. Damascus University, Syria, PO.box: 31037, Damascus; E-mail: ameer.kakaje@hotmail.com

Abstract

Hyper IgE syndrome (HIES) is a medical condition that can be sporadic or hereditary. It consists of multiple overlapping primary immunodeficiency conditions and is characterized by a classical triad of high immunoglobulin E (IgE) levels, recurrent pneumonia with pneumatocele and recurrent cold skin abscesses from staphylococcus infections. Eosinophilia is also common in HIES patients. HIES is often underdiagnosed in Syria as it cannot be confirmed without genetic testing, which is unavailable across Syria for HIES. We present the first case from Syria of a suspected child with HIES that has some additional distinct features. Other cases in a regional country carried atypical novel mutations, which may indicate that these mutations may exist in Syria as well. However, our case had findings that were not reported with other HIES cases. Determining these genes in the case presented was not possible, and future studies need to overcome this hurdle.

INTRODUCTION

Hyper IgE syndrome (HIES) is a rare hereditary primary immunodeficiency. It is characterized by a classical triad of high immunoglobulin E (IgE) levels, recurrent pneumonia with pneumatocele and recurrent cold skin abscesses from staphylococcus infections [1]. Patients also suffer from chronic candidiasis and have ophthalmic manifestations such as conjunctivitis, spontaneous corneal perforation and strabismus [1]. While most cases of HIES are sporadic, some case can be familial with an autosomal dominant or recessive pattern [2].

HIES is caused by multiple gene defects, some of which are still being studied, and novel mutations were found in Lebanese families who had a few distinct features than typical HIES [3]. These mutations may also exist in Syria as it neighbors Lebanon, and they both share a common background.

CASE REPORT

A 17-year-old male came with swollen left knee and forefinger. He previously had diagnosed with multiple cold abscesses. The child has consanguineous parents as they were first cousins. The patient also had itchy eczematous and desquamating eruptions on the trunk and scalp around the age of six months. Atopic dermatitis was subsequently diagnosed and managed conservatively. By the age of two, the patient had a pea-sized lateral abscess in the neck that reached the size of a golf ball in one year. It was managed by antibiotics and drainage with culture yielding *Staphylococcus aureus*. Afterwards around the age of five, an abscess was formed on the scalp behind the ear, which was also caused by *Staphylococcus aureus*. By the age of six, an abscess was formed on the skin on the right parotid gland. By the age of ten, an abscess was formed in the groin extending to the right

†Ameer Kakaje, http://orcid.org/0000-0002-3949-6109
Damascus University does not have official emails and therefore only private emails were used Ameer Kakaje list of publications: https://scholar.google.com/citations?user=e0iktHUAAAAJ&hl=en

Received: May 28, 2020; **Revised:** July 20, 2020; **Accepted:** September 11, 2020

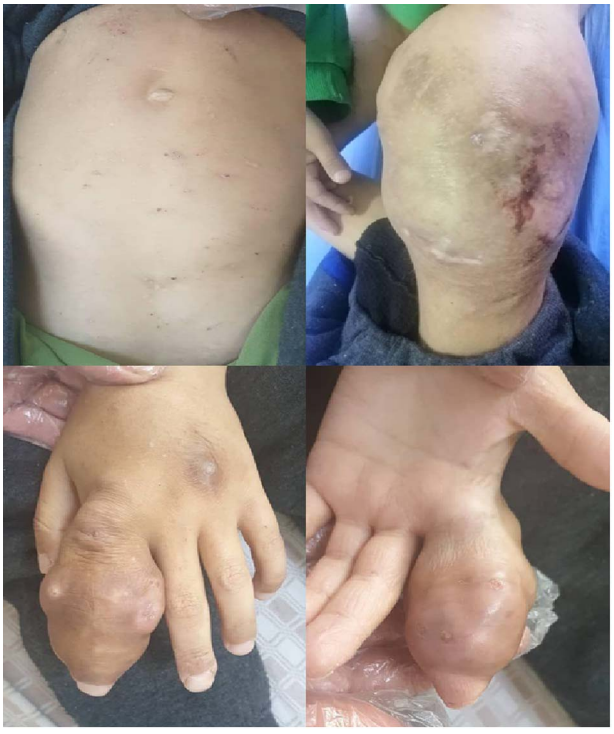

Figure 1: It demonstrates the lesions on the knee and finger and the multiple scars on the abdomen.

scrotum. Around the age of 12, an abscess that grew *Staphylococcus aureus* was formed on the lateral side of the left thigh, and the knee was also swollen. Finally by the age of 14, the patient had a swollen left forefinger. The histopathology revealed a xanthoma in the scalp and xanthogranuloma with abscess formation in the salivary gland with no malignant or tuberculosis features. The patient declared that he had normal teeth development and no ophthalmological symptoms. No history of pneumonia was noted. Family history was also insignificant.

On examination, the current swelling on the knee and forefinger were solid, non-tender and not warm to touch (Fig. 1). The patient had minor desquamating and peeling skin over the soles and palms. No scoliosis was noted, but the patient had a distinguished facies (Fig. 2). He had a broad nasal bridge, a depressive asymmetric face, a mild prognathism and coarse features. He was in a good general condition and had a good appetite. However, the patient was pale and had a short stature (147 cm), which was nearly four standard deviations (SD) below the mean height of his parents with no signs of puberty (Tanner I). No oral thrush was noted, and teeth examination was normal. There was no lymphadenopathy or hepato-splenomegaly.

The patient had normal WBCs count, platelet count, electrolytes, urine analysis and lipid profile, but eosinophil count was 541 cells/mcl, he had microcytic anemia Hb (6.4 g/dl) and MCV was (54 fl). Blood film showed hypochromic microcytic red blood cells, and an increased eosinophil count (10%). Hemoglobin electrophoresis and tuberculosis Mantoux test were normal. Serum protein electrophoresis showed a high gamma protein level, with low alpha 1 and albumin levels, and a total complement protein level (ch50) of 59 U/ml ($n > 23$), IgE: 2780 IU/ml ($N < 100$), IgG: 2773 (N: 700–1600), IgM: 184 (N: 40–230). Chest X-ray was normal. Knee and finger X-rays revealed an enlargement of soft tissue with intact bones (Fig. 3). Knee MRI

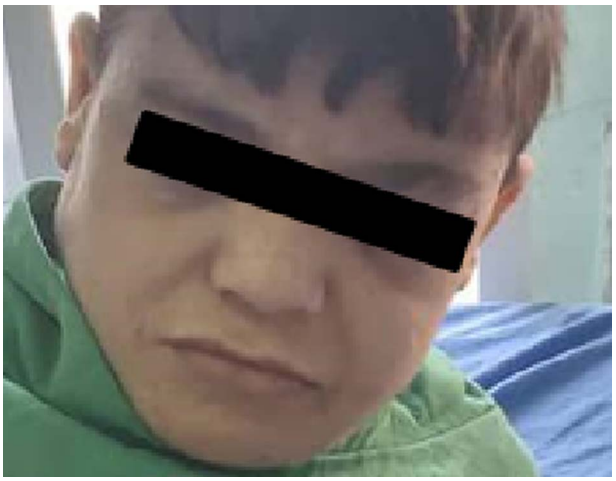

Figure 2: It demonstrates the distinguished facies of the child.

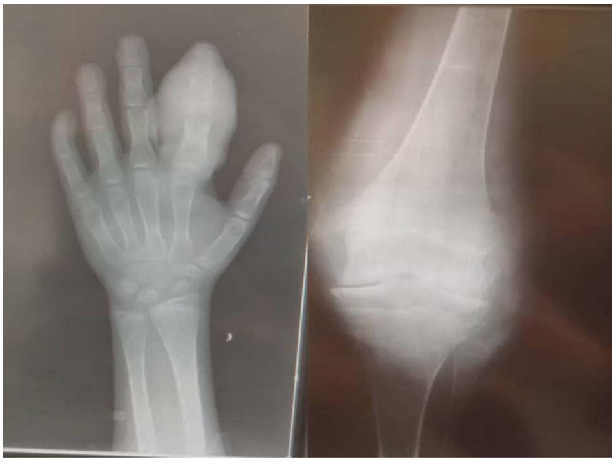

Figure 3: It demonstrates the X-rays of the knee and finger.

showed a subcutaneous loculated effusion, and hematomas in the sub- and supra-patellar and the popliteal fossa. MRI of the head was normal with a normal pituitary stalk and no thickening. MRI of the neck (Fig. 4) demonstrated an elliptical segmented lesion with thick walls in the right parapharyngeal space that measured $5 \times 6 \times 8$ cm, which was suggestive of an abscess. The patient scored around 33 on the Grimbacher et al. 1999 scale for assessing HIES [4], which was indicative of a possible STAT3-deficient HIES [5].

In the hospital, the patient stayed for three weeks and developed pneumonia that was improved with empirical antibiotics consisting of vancomycin and meropenem. The patient was discharged and was given trimethoprim/sulfamethoxazole (TMP-SMX) as prophylaxis against staphylococcus, but follow-ups could not be attended due to the COVID-19 outbreak.

DISCUSSION

HIES consists of multiple overlapping primary immunodeficiency conditions, each of which has its distinct features. The most common defects are a deficiency of signal transducer and activator of transcription 3 (STAT3), and a deficiency of dedicator of cytokinesis 8 (DOCK8) [6]. Genetic testing is considered the

Table 1: xxxx

Clinical findings	POINTS[a] 0	1	2	3	4	5	6	7	8	10	Patient's score
Highest serum-IgE level (IU/ml)[b]	< 200	200–500			501–1,000				1,001–2,000	>2,000	10
Skin abscess	None		1–2		3–4				>4		8
Pneumonia (episodes over lifetime)	None		1		2		3		>3		
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele		
Retained primary teeth	None	1	2		3				>3		
Scoliosis, maximum curvature	< 10°		10–14°		15–20°				>20°		2
Fractures with minor trauma	None				1–2				>2		
Highest eosinophil count (cells/µl)[c]	< 700			700–800			>800				6
Characteristic face	Absent		Mildly present			Present					5
Midline anomaly[d]	Absent					Present					
Newborn rash	Absent				Present						
Eczema (worst stage)	Absent	Mild	Moderate		Severe						4
Upper respiratory infections per year	1–2	3	4–6		>6						4
Candidiasis	None	Oral	Fingernails		Systemic						
Other serious infections	None				Severe						
Fatal infection	Absent				Present						
Hyperextensibility	Absent				Present						
Lymphoma	Absent				Present						
Increased nasal width[e]	<1SD	1-2SD		>2SD							1
High palate	Absent		Present								2
Young-age correction	>5 years			2–5 years		1–2 years		≤1 year			

[a]The entry in the furthest-right column is assigned the maximum points allowed for each finding. [b]Normal < 130 IU/ml. [c]700/µl = 1 standard deviation (SD), 800/µl = 2 SD above the mean value for normal individuals. [d]For example, cleft palate, cleft tongue, hemivertebrea, other vertebral anomaly, etc. (see Grimbacher et al. [1999]). [e]Compared with age- and sex- matched controls [see Farkas et al. 1994].

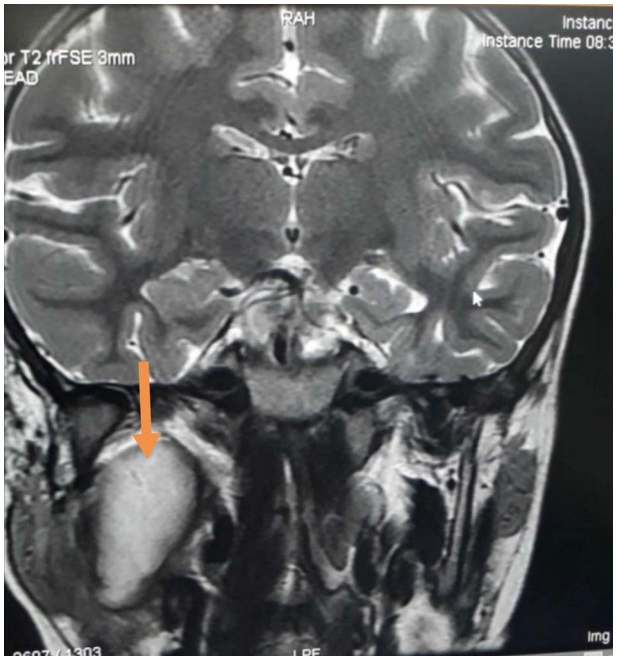

Figure 4: MRI of the head and neck showing the lesions in the neck (arrow).

golden standard for STAT3-deficient HIES while Th17 cells testing can be used for a probable HIES, and a scoring system [4] is used for a probable STAT3 mutation [5]. The patient got 10 points for the IgE level, 8 for the number of abscesses, 3 for the eosinophil count, 5 for the congenital anomalies, 4 for the congenital rash, 2 for the eczema and 1 for the wide nose. In total, the patient got 33. We can also add one point for the confirmed pneumonia.

Diagnosis can be problematic as there is no clear criteria and symptoms are quite diverse similar to our case. However, most clinicians diagnose HIES with its clinical features, and the scoring system is used to evaluate for STAT3 probability [5]. We could not identify the mutations due to the unavailable genetic testing for HIES in Syria and the financial disadvantage, which affected many other cases and have delayed diagnosis and treatment [7, 8].

The most common locations for cold abscesses are the face and the trunk. Pulmonary complications exist in 77% of cases, which were absent in our case. Patients can have distinctive coarse facies features that become universal by 16 years of age, including asymmetrical faces, hemitrophy, prominent foreheads, broad nasal bridges, mild prognathism and deep-set eyes (Fig. 2) [1]. Scoliosis can also occur in 63% of cases, and all patients have some degree of eczema. Prophylactic antibiotics against staphylococcus can be used such as TMP-SMX as reoccurrence is not uncommon [1]. However, as HIES was not diagnosed the patient did not take staphylococcus prophylaxis in previous visits.

In one study on Lebanese participants with HIES, two sporadic mutation carriers were of consanguineous parents [3]. This is similar to our patient who had consanguineous parents with no history of HIES in the family. Our patient also had arthropathy of the knee, hematomas and a cold abscess in the parapharyngeal space, which are different from the Lebanese patients. Moreover, the patient had unexplainable xanthoma and hematomas, which are atypical for HIES.

The eczema in HIES is difficult to be distinguished from atopic dermatitis. However, a long course from early life with atypical distribution such as in the axilla and groin, recurrent staphylococcus infections with cold abscesses and resistant to conventional treatment are signs of HIES dermatitis rather than atopic dermatitis [1]. Our case had peeling skin over the soles and palms and was diagnosed with atopic dermatitis in infancy. One of the most important differential diagnosis for xanthomas is Langerhans cell histiocytosis, which can present with consistent eczema, and unexplained skin lesions. However, histology and immunophenotyping were not suggestive in our case. Our

patient did not have pituitary manifestations, stalk thickening or diabetes insipidus, which can be seen in Langerhans cell histiocytosis [9]. Other differential diagnoses include aspergillosis, and other immune deficiencies such as Wiskott–Aldrich syndrome (WAS). WAS is an immunodeficiency disorder that is characterized by eczema, thrombocytopenia, recurrent infections and high IgE levels [10]. The patient had recurrent cold staphylococcus abscesses and did not have the other features of WAS, which made the diagnosis highly unlikely [10].

In conclusion, HIES is a rare disease that is understudied and underdiagnosed in Syria although there is a high potential for novel mutations in the region. Despite our case having many typical HIES features, xanthoma and knee hematomas were unique. This study provides an insight into HIES for physicians in the region and encourages future work on the matter.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was taken for this research. Our study ethical aspects were reviewed and approved by Damascus University deanship, Damascus, Syria.

CONSENT FOR PUBLICATION

Consent for using and publishing the data was taken before participating in the research.

AVAILABILITY OF DATA AND MATERIALS

The data can be made available upon reasonable request.

CONFLICT OF INTEREST STATEMENT

We have no conflict of interest to declare.

FUNDING

No funding was received for this study. We did not receive any support in forms of grants, equipment or drugs. This work was conducted in Al Mouwasat University Hospital.

GUARANTOR

Dr Rama Awad is the guarantor for the images and the case.

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