CASE REPORT

A rare primary immunodeficiency

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SUMMARY

A 9-year-old girl presented with failure to thrive, chronic mucopurulent nasal discharge, recurrent skin pustules and recurrent episodes of purulent ear discharge since 2 years of age. She had coarse facial features with extensive eczema, multiple pyoderma scars, florid dental caries, retained primary dentition, hypermobile joints and a woody induration of the vulva. Autosomal dominant hyper-IgE syndrome was suspected and confirmed by very high serum IgE levels. Vulval biopsy revealed a premalignant condition. STAT 3 mutation, which is usually responsible for this condition, was not found in our case, indicating an as yet unidentified mutation. The child also had unusual features like the total absence of clinical and radiological features of pneumonia. The premalignant change in the vulva was also unusual since vulval carcinoma has not been reported so far in children with this disorder. This child will require a close follow-up to look for malignant transformation.

BACKGROUND

Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency disorder characterised by chronic dermatitis, recurrent skin and lung infections and elevated serum IgE levels. With recent advances in genetic studies, several mutations have been discovered in relation to HIES. The two most common types are an autosomal dominant (AD) variety with mutation in the STAT 3 (signal transducer and the activator of transcription 3) gene and autosomal recessive (AR) form due mainly to a mutation in the DOCK 8 (dedicator of cytokinesis 8) gene. Though the child reported here had features consistent with AD-HIES, genetic analysis did not report a STAT 3 mutation, indicating an as yet unrecognised mutation.

CASE PRESENTATION

A 9-year-old girl child, born to third degree consanguineous parentage, was brought with symptoms of chronic mucopurulent nasal discharge, recurrent skin pustules and recurrent purulent ear discharge since 2 years of age. She had dry skin for the past 3 years, vulval swelling for the past 2 years and failure to gain weight and height. In the past, she had diarrhoea until 5 months of age and a fracture dislocation of the right elbow at 4 years. However, there was no episode of pneumonia. On examination, she had coarse facial features ([figure 1](#)) with dry, rough skin, eczema, seborrhoeic dermatitis, multiple healed pyoderma scars, florid dental caries ([figure 2](#)), central perforation in the left ear, goitre and retained primary dentition. Systemic examination showed

Figure 1 Coarse facies.

splenomegaly, bilateral indurated vulval enlargement ([figure 3](#)) and hypermobile joints (Beighton score 9/9; [figure 4](#)). She secured a score of 54, using the National Institutes of Health (NIH) scoring system for HIES, and hence a definitive clinical diagnosis of AD-HIES was made ([table 1](#)).¹

Figure 2 Florid dental caries.

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Figure 3 Indurated vulval enlargement.

INVESTIGATIONS

As the clinical features were suggestive of a primary immunodeficiency disorder, her immunoglobulin profile was performed which showed very high levels of IgE (4000 IU/mL) and normal levels of other immunoglobulins along with evidence of normal cellular immunity. The absolute eosinophil count was 370 cells/mm³ and the nitroblue tetrazolium test, for neutrophil function, was normal. Thyroid function test, chest X-ray and echocardiography were normal. MR angiography did not reveal any vertebral artery aneurysm. Vulval biopsy showed a premalignant

lesion, namely, lichen sclerosus et atrophicus with mild epidermal hyperplasia (figure 5). No fungal elements were identified in the specimen.

Genetic analysis for a STAT3 mutation was negative.

TREATMENT

This child has been started on prophylactic doses of cotrimoxazole and itraconazole to prevent recurrent skin and sinopulmonary infections. She was also prescribed emollients for dry skin, bleach baths for prevention of staphylococcal infection and antihistamine for the control of pruritus.

OUTCOME AND FOLLOW-UP

The child is on regular follow-up and we plan to get periodic echocardiograms and brain MRI to detect vascular complications at the earliest. We also plan to repeat the vulval biopsy annually to detect any malignant transformation.

DISCUSSION

HIES is a rare primary immunodeficiency disorder, whose diagnosis is difficult in children. It is characterised by recurrent skin boils, eczematoid dermatitis, cyst forming pneumonia and extreme elevation of IgE level.^{2,3} STAT3 mutation (signal transducer and the activator of transcription 3) is responsible for most of the familial and sporadic cases of AD-HIES.² STAT3 is a major signal transduction protein required for normal wound healing, angiogenesis, immune pathways and for protection against cancer.⁴ Hence, a mutation of STAT3 results in aberrant wound healing and angiogenesis, immunodeficiency and an increased predisposition to malignancies.^{4,5}

This condition classically manifests with recurrent respiratory tract infections and skin boils. It is a disease characterised by evidence of both excess and too little inflammation. The release of proinflammatory (IL6) and anti-inflammatory (IL10) cytokines

Figure 4 Hypermobile joints with a Beighton score of 9/9.

Table 1 NIH scoring system with clinical and laboratory tests for related individuals with HIES

Clinical features	Points											Index case
	0	1	2	3	4	5	6	7	8	9	10	
Highest serum IgE level	<200	200–500			500–1000				1001–2000		>2000	10
Skin abscesses	None		1–2		3–4				>4			8
Pneumonia	None		1		2		3		>3			0
Parenchymal lung disease	Absent						Bronchiectasis		Pneumatocele			0
Retained primary teeth	None		2		3				>3			8
Scoliosis	<10°		10–14°		15–20°				>20°			2
Fractures with minor trauma	None				1–2				>2			4
Highest eosinophil count	<700			700–800			>800					0
Characteristic face	Absent		Mildly			Present						5
Midline anomaly	Absent					Present						0
Newborn rash	Absent				Present							0
Eczema	Absent	Mild	Moderate		Severe							4
URI/year		3	4–6		>6							4
Candidiasis	None	Oral	Fingernails		Systemic							0
Other serious infections	None				Severe							0
Fatal infections	Absent				Present							0
Hyperextensibility	Absent				Present							4
Lymphoma	Absent				Present							0
High palate	Absent		Present									2
Increased nasal width	<1 SD	1–2 SD		>2 SD								3
Young age correction	>5 years			2–5 years		1–2 years		≤1 years				0
											Total	54

Score of ≥15—likely to carry the HIES genotype, 10–14—indeterminate, <10—unlikely to carry the HIES genotype.
HIES, hyper-IgE syndrome; NIH, National Institutes of Health; URI, upper respiratory tract infection.

Figure 5 Vulval biopsy showing Lichen Sclerosus et atrophicus.

has been implicated, thus explaining the protean manifestations.^{2,4} A classical example of excess inflammation is the aberrant healing process following staphylococcal pneumonia leading to pneumatocele formation and bronchiectasis. Though the occurrence of recurrent staphylococcal pneumonia is the clinical hallmark of AD-HIES,^{2,6} the child reported had an unusual absence of any clinical or radiological evidence of pneumonia to date. On the contrary, skin boils manifested typically in this child with a classical absence of inflammatory signs. These are the so-called ‘cold skin abscesses’ indicating too little inflammation.^{2,4}

Skeletal features in this child include a history of pathological fracture dislocation, a characteristic manifestation of AD-HIES, as a result of osteopenia.^{4,5} She also had significant hypermobility with a Beighton score of 9/9, which is well documented in the literature in as many as 68% of cases,^{2,3} and may presage the development of scoliosis and degenerative joint disease.⁴

The presence of supernumerary teeth, in our case, is the result of retention of primary dentition. This probably results from the reduced resorption of tooth roots, thus delaying the eruption of permanent teeth. Normal eruption follows extraction of temporary dentition.⁴

Vascular abnormalities like tortuosity and aneurysm, a common association with AD-HIES, is attributable to vascular remodelling rather than inflammation, resulting in arterial fragility.² In the child reported, though the initial echocardiogram and MR angiogram were normal, periodic reassessment to detect any vascular complications will be needed.

Though this child has skeletal and immunological features of AD-HIES with an NIH score of 54 (indicating definite disease), contrary to expectation, STAT 3 mutation was not found on genetic analysis. In the absence of STAT 3 mutation, the other differential diagnosis entertained was AR-HIES. Though both the conditions have elevated IgE levels, the characteristic facies, skeletal abnormalities and retained primary dentition seen in this child are not seen in AR-HIES. Furthermore, florid viral infections of the skin and neurological complications, typical of AR-HIES, were also conspicuously absent.⁴

It was noted that around 5% of the individuals who satisfy clinical criteria for AD-HIES may not have an identifiable STAT

3 mutation, thus supporting the argument that a mutation at an as yet unidentified locus exists, which may be the case in our child.^{3,7,8} Though malignancies including non-Hodgkin's lymphoma, Hodgkin's lymphoma, pulmonary adenocarcinoma and squamous cell carcinoma are reported in AD-HIES, according to some studies, in the majority of reported cases with malignancies STAT 3 mutation was not made out.⁹ The child reported had a woody vulval lesion with histopathology suggestive of lichen sclerosis et atrophicus, which is a premalignant condition, thus reiterating the fact that there still remains some unidentified mutation responsible for this condition besides the newly discovered STAT 3 mutation.^{3,6}

Though vulval carcinoma has been reported in adults with AD-HIES, there have been no such reports in children.^{10,12} Since our case already has a premalignant condition of the vulva at such a young age, a close follow-up is required for detecting malignant transformation of this lesion.¹³

We conclude that all cases with clinical and immunological features consistent with AD-HIES may not have the STAT 3 mutation. A variant form of AD-HIES, with a mutation at an unidentified locus, must exist, which may be the case in the child reported here.

Learning points

- ▶ Screen all children with recurrent eczema, otitis media and pyoderma for hyper-IgE syndrome (HIES).
- ▶ Autosomal dominant (AD) HIES may present without pulmonary involvement.
- ▶ Vulval induration may presage a malignant transformation to carcinoma.
- ▶ Absence of the STAT 3 mutation does not rule out AD-HIES.

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