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Case Report

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Diagnosing hyper-IgE syndrome in adulthood: A case based discussion in resource-limited setting

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Abstract

Hyper-IgE syndrome (HIES) in adult patients is a very rare occurrence with heterogeneous clinical manifestations. Most of the previously described cases were from developed countries, capable of performing comprehensive testing to pinpoint the underlying genetic defect. Such a facility is often unavailable in resource-limited countries, creating a great diagnostic challenge. Nevertheless, several important clinical clues can significantly aid in hypothesis formulation, such as the presence of primary immunodeficiency, eosinophilia, and a history of atopy. We describe the process of diagnosing HIES on an 18-year-old Asian male through systematic symptom analysis and strategic use of a simple laboratory examination.

Keywords: hyper-IgE syndrome; DOCK8; adulthood; clinical diagnosis; primary immunodeficiency

1. Introduction

Hyper-IgE syndrome (HIES) in adult patients is a very rare occurrence with heterogeneous clinical manifestations. There is very limited existing literature on the subject, most of which describes cases from developed countries with facilities to perform comprehensive genetic testing (1-4). The scarcity of such technology, combined with the absence of strong clinical diagnostic criteria, often causes misdiagnosis and sub-optimal treatment, especially in resource-limited countries (5,6). Nevertheless, several important clinical clues can significantly aid in hypothesis formulation, such as the presence of primary immunodeficiency, eosinophilia, and a history of atopy. We describe a case of 18-year-old Asian male suffering from primary immunodeficiency with eosinophilia, clinically diagnosed as HIES.

2. Case Presentation

An 18-year-old Asian male suffered from progressively declining health over a four-month period. He was a previously healthy individual with no history of severe infection, allergic reaction, as well as hospitalization. He had normal growth and development as a child. He was an only child with no significant history of familial disease. He initially suffered recurrent abdominal pain, which was diagnosed as appendicitis. He underwent an appendectomy and experienced repeated post-operative wound dehiscence. One month after surgery, he experienced a pruritic rash on his back which spread to most of his body and facial edema after consuming a multivitamin product consisting of vitamin B1, B12 and vitamin C. Most of the rash and edema resolved after cessation of the aforementioned multivitamin. However, the skin around his right thigh worsened and started to show signs of ischemia. He also started to develop persistent diarrhoea, roughly 5-7 times daily with feces of a consistency of type 7 on Bristol stool scale. The wound on his right thigh eventually developed a secondary infection and he fell into septic shock, causing a grade 3 acute kidney injury requiring dialysis. He had lost roughly 15 kg in 3 months and looked cachexic. His physical examination was unremarkable except for the wound on his right thigh (Fig. 1).

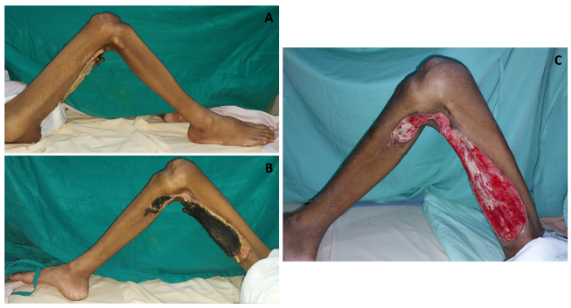

Fig. 1. Non-healing wound on patient's right thigh taken before (A, B) and after surgical debridement (C).

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No lymphadenopathy was detected on physical and ultrasound examination. His bloodwork showed an absolute eosinophil count of 7000 cells/µL with negative tests for HIV, TBC, and ANA-IF. His IgE level was >2500 kIU/L with a specific IgE level elevated only towards shellfish (24.5 kIU/L). His stool analysis showed fungal infestation, and his wound culture isolated *Pseudomonas stutzeri* and *Candida tropicalis*. Genetic testing wasn't available for our patient. However, he had a DOCK8 score of 49.08, which predicted DOCK8 mutation (Table 1).

Table 1. The DOCK8 score. A total number of scaled points > 30 predicts a DOCK8 mutation (7)

			Feature	Points x Scale		Scaled points
1	**Mandatory: IgE> 10x normal range**					
2	A	Parenchymal lung abnormalities	No structural lung damage	0	-5.00	0.00
			Bronchiectasis	6	-5.00	-30.00
			Pneumatoceles	8	-5.00	-40.00
	B	Highest eosinophiles/µl	< 700	0	8.18	0.00
			701-800	3	8.18	24.54
			>800	6	8.18	49.08
	C	Sinusitis, otitis (# episodes in worst year)	1-2	0	15.50	0.00
			3	1	15.50	15.50
			4-6	2	15.50	31.00
			>6	4	15.50	62.00
	D	Retained primary teeth	None	0	-4.54	0.00
			1	1	-4.54	-4.54
			2	2	-4.54	-9.08
			3	4	-4.54	-18.16
			>3	8	-4.54	-36.32
	E	Fractures with minor trauma	0	0	-9.09	0.00
			1-2	4	-9.09	-36.36
			>2	8	-9.09	-72.72
			Total (Sum A-E) Scaled points			49.08

*IgE: Immunoglobulin E

He was treated empirically with meropenem 1 gram TID and was adjusted according to the culture result to ampicillin-sulbactam 375 mg BID with fluconazole 150 mg QD, as well as fluid and nutritional support. He was prescribed methyl prednisolone 31.25 mg QD during septic shock and was tapered as his condition stabilized to 8 mg QD. His septic shock and kidney injury were resolved after 3 weeks. Surgical wound debridement and biopsy were performed, followed by vacuum-assisted wound closure. The wound biopsy result showed non-specific suppurative inflammation with no sign of vasculitis and eosinophilic infiltration (Fig. 2). On discharge, his condition was stable with signs of improved wound healing. His IgE level and absolute eosinophil count improved to 370 kIU/L and 500 cells/µL, respectively.

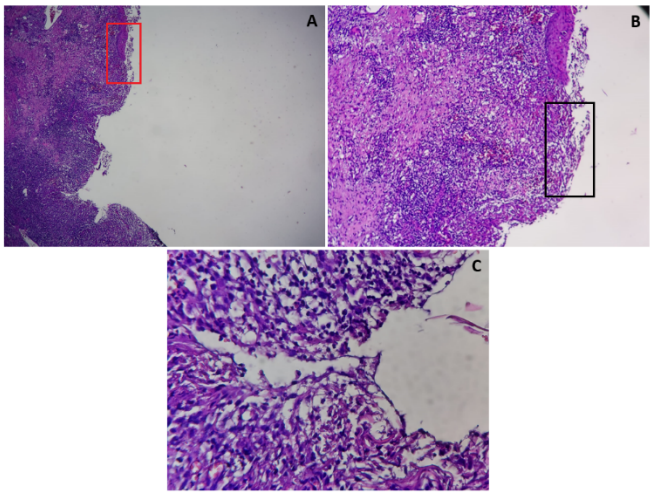

Fig. 2. Hematoxylin and eosin-stained skin biopsy taken during surgical debridement showing lymphocyte and neutrophil infiltration, suggesting non-specific suppurative inflammation. There were no signs of vasculitis or eosinophilic infiltration. Magnifications: A: 4x; B: 10x of the red rectangle, and C: 40x of the black rectangle.

3. Discussion

To date, more than 400 types of PIDs have been described with overlapping clinical manifestation, requiring comprehensive genetic testing to reach a definitive diagnosis, which was not available in our region. Due to fund and resource limitations, we had to strategically chose which diagnostic modality to use and exclude most of the differential diagnoses (DDx) clinically. Firstly, we reduced the DDx substantially by including only PIDs with eosinophilia in adulthood, which includes, but not limited to: HIES, Wiskott Aldrich syndrome (WAS), immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, and Netherton's syndrome, autoimmune lymphoproliferative syndrome (ALPS), selective IgA deficiency, and adenosine deaminase (ADA) deficiency (8). Secondly, we performed an IgE level examination due to the possible allergic reaction preceding the patient's skin lesion, which showed an extremely high level of >2500 kIU/L with a specific IgE level elevated only towards shellfish (24.5 kIU/L). We excluded WAS due to normal platelet level, IPEX syndrome due to absence of endocrinopathy, Netherton's syndrome due to absence of typical ichthyotic skin and bamboo hair shaft defects, ALPS and ADA deficiency due to normal lymphocyte count and morphology, while extremely elevated IgE level that had never been described in selective IgA deficiency, leaving HIES as the best fitting diagnosis (8,9).

Table 2. The HIES Score. A total score of >40: likely , 20-40: uncertain of HIES (10)

CLINICAL FINDINGS	Points									
	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/ml)	< 200	200-500			501-1000				1001-2000	>2000
Skin abscesses	None		1-2		2-3				>4	
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	$< 10^0$		$10\text{-}14^0$		15-20				> 20	
Fractures with minor trauma	None				1-2				>2	
Highest eosinophil count/µl	< 700			700-800			> 800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections/year	1-2	3	4-6		> 6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width	< 1 SD	1-2 SD		> 2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2-5 years		1-2 years		≤ 1 year		
Total	20									

*IgE: Immunoglobulin E

According to its inheritance pattern, HIES can be broadly categorized as AD, AR, or sporadic form (1,10,11). Our patient didn't fit the somatic description of classical AD-HIES due to STAT3 deficiency, which usually presents in childhood (Table 2) (10,12). On the other hand, our patient had the immunological characteristics of HIES, such as: IgE level > 2000 kIU/L, eosinophilia, a history of atopy, mucocutaneous candidiasis, severe skin infection, and GI malabsorption, which matched the characteristics of AR-HIES, especially DOCK8 immune deficiency syndrome (DIDS) (12-14). Furthermore, the result of DOCK8 scoring in our patient clinically supports the diagnosis of DIDS (Table 1). Similar to other forms of HIES, clinical manifestation of DIDS tend to occur in childhood (7). While significantly less frequent, DIDS in adulthood have previously been reported with cutaneous manifestations and atopy being the most dominant complaints (2,7). Chronic diarrhoea is frequently observed in DIDS and is caused by malabsorption due to intestinal infection and allergic or autoimmune enteropathy, which might lead to malnutrition and failure to thrive (14,15). Poor wound healing in DIDS can be caused by IL-22 deficiency, causing apoptosis and proliferation inhibition of intestinal cells (16). Although, other factors such as infection and malnutrition might also contribute to poor wound healing in this patient. Hematopoietic cell transplantation is the only curative treatment for AR-HIES and DIDS, whereas no curative treatment is currently available for AD-HIES (17,18). Antibiotic and antifungal agents are routinely given regardless of the type of HIES (19). In the absence of facility to perform comprehensive genetic examination, diagnosis of HIES can still be achieved through systematic symptom analysis and strategic use of simple laboratory examination. Antibiotic and antifungal agents are the mainstay of HIES management and can be given regardless of the type of underlying genetic mutation.

Conflict of interest

The authors declared no conflict of interest.

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Written informed consent was obtained from the patient for the publication of this case report and the accompanying data.

Authors' contributions

Concept: D.P.M., B.L., D.P.W., N.R., M.J., Design: D.P.M., B.L., N.R., Data Collection or Processing: D.P.M., B.L., Analysis or Interpretation: D.P.M., B.L., D.P.W., N.R., M.J., Literature Search: D.P.M., B.L., Writing: D.P.M., B.L., D.P.W., N.R., M.J.

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