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Letter to Editor

Paediatrics Section

Hyper IgE Syndrome

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Dear Editor,

Immunodeficiency syndromes are considered very complicated diseases and usually, clinicians find them intimidating. However, if pattern of infections and associated clinical features are kept in mind then we can diagnose many of these disorders with the help of a thorough history and physical examination assisted by few diagnostic tests without needing sophisticated and costly investigations like genetic testing.

Hyper IgE Syndrome (HIES) also known as Job's Syndrome is a rare primary immunodeficiency disorder characterised by recurrent cutaneous cold abscesses, sinopulmonary and skin infections and associated elevated IgE level (>2000 IU/mL), along with connective tissue and skeletal abnormalities [1].

A six-month-old male child born of the non-consanguineous marriage, normal perinatal and family history, presented with multiple skin abscess (at thigh, scapular region and axillary region with minimal signs of inflammation and features suggestive of pneumonia. Systemic examination was unremarkable except for mild eczematous changes of face. Investigations sent were suggestive of acute bacterial infection (Raised total leucocyte count (21000/mm^3) with neutrophilia (80%) and highly positive C-Reactive Protein (86 mg/L). Platelet count was normal and blood culture sent was sterile. Injection Amoxicillin-Clavulanic acid were started, incision and drainage was done and pus sent for culture which grew Methicillin Resistant *Staphylococcus Aureus* (MRSA) sensitive to vancomycin, linezolid and resistant to amoxicillin-clavulanic acid, ciprofloxacin, amikacin. Antibiotics were upgraded as per sensitivity to Injection Vancomycin, which was continued for 10 days and daily povidone-iodine dressing was done. Patient responded well to treatment and was discharged after two weeks in fair condition with all abscess and pneumonia completely resolved.

Two months later, the child again presented to us with similar complaints but with greater severity this time. He came in a sick general condition with cellulitis of left thigh, severe bronchopneumonia and abscess at multiple sites including anterior neck and gluteal region. Child was started on injection vancomycin and piperacillin-tazobactam, which were continued for 12 days. Pus was drained under ultrasonographic guidance for neck abscess and incision and drainage was done for other abscesses, along with supportive care. Though blood culture was sterile again but pus culture grew MRSA with sensitivity pattern similar to previous culture. In view of recurrent episodes of the infections immunodeficiency was suspected and child was investigated for causes of primary and secondary immunodeficiency. Work-up was sent for tuberculosis, diabetes mellitus, fungal infection, HIV and peripheral smear for abnormal cells to rule out haematological malignancies. Bone marrow and cerebrospinal fluid examination was also performed which was within normal limits. Rest of investigations was normal except for eosinophilia in the blood count (absolute eosinophil count=850/µL). In view of repeated cold abscess, bronchopneumonia along with raised eosinophil count, a possibility of Hyper IgE syndrome arose. Serum IgE levels were sent and value of 3500 IU/mL was obtained. Due to resource constraints, confirmatory genetic studies could not be done, but a diagnosis of Hyper IgE syndrome was confirmed clinically according to National institute of health (NIH) scoring utilising various clinical features [Table/Fig-1] NIH score of the index patient was 44 in patient suggesting a diagnosis of Autosomal dominant HIES [2].

After treating the abscess and bronchopneumonia patient was discharged on prophylactic co-trimoxazole, along with skin care advice (chlorhexidine baths), vitamin D supplementation (to prevent osteopenia), and immunisation guidance. Patient was normal on subsequent follow-ups at one and three months.

First described in 1966 by Davis SD et al., the Hyper IgE Syndrome is a rare multi-system immunodeficiency disorder. Incidence cannot be determined due to rarity of the disease [3]. Mostly, it is an autosomal dominant condition but recently autosomal recessive variant has also been described with absence of connective tissue and skeletal anomalies typical of Autosomal Dominant HIES and increased incidence of viral skin infections [4]. Autosomal dominant variant is caused by mutation in *STAT3* gene located at long arm of Chromosome 17 [5].

Some patients with Autosomal Recessive Hyperimmunoglobulin E Syndrome (ARHIES) have mutations in DOCK8 which has important role in T and B cell development and functions and its deficiency is now known to cause a combined immunodeficiency rendering the affected patients susceptible to viral, fungal, and bacterial infections. ARHIES is distinguished by recurrent sinopulmonary infection, severe cutaneous viral infection often caused by Herpes simplex viruses, human papilloma virus, herpeszoster virus, and molluscum contagiosum virus in addition to elevated IgE and lack features involving the skeletal system [6,7].

Chronic and recurrent lung infections lead to complications like bronchiectasis. Skeletal anomalies include scoliosis, osteopenia, minimal trauma fractures, hyperextensiblity and degenerative joint disease. Failure of exfoliation of primary teeth, cardiac and brain aneurysms and malignancies are other associations. Septicaemia is the main cause of death [8].

Management strategies include injectable and oral antibiotics for duration depending on severity of infection, aggressive skin care and prophylactic antibiotics. Immunomodulatory therapy and bone marrow transplantation are being explored as therapeutic option [9].

Recently different immunomodulators have been tried for HIES. Interferon-gamma has been used with mixed results [10]. Cyclosporine and histamine-2 receptor are also being explored as therapeutic options [11,12]. Levamisole which stimulates T cell and Natural Killer (NK) cell function was found to be inferior to placebo [13]. Intravenous Immunoglobulin (IVIG) may decrease the number of infections for some patients [14].

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

[Table/Fig-1]: NIH score of the case.
<20 is considered unlikely to indicate AD-HIES;
20-40 is considered indeterminate;
Score>40 is suggestive of AD-HIES

This case illustrates that with the help of a complete history and thorough physical examination a clinician can diagnose rare disease like immunodeficiency even without aid of sophisticated testing.

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