CPC CORNER

A 3.5 years old boy with recurrent skin infections

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Case Representation

Dr Bushra Rasool: A 3.5-year-old boy presented to the outpatient department with complaints of multiple abscesses and boils, bilateral ear discharge, itchy skin rash, oral ulcers, and recurrent chest infections since 6 months of age.

In the outpatient department, the patient presented with multiple painful abscesses and boils, predominantly in the cervical and axillary regions, associated with low-grade fever and bilateral purulent, foul-smelling ear discharge.

The patient had been well for the first 6 months of life, after which he began developing multiple abscesses and boils on his body, accompanied by low-grade fever. Since the age of one year, he has experienced intermittent oral thrush. There have been complaints of foul-smelling ear discharge and itchy skin rash for 1.5 years of age. He has a history of recurrent chest infections and has visited multiple clinics, with two admissions to a local hospital for similar complaints. His parents are first cousins, and he has a one-year-old younger sister; there is no history of sibling death. Birth history was insignificant, with no history of delayed shedding of the umbilical cord. He achieved developmental milestones at the appropriate times, was vaccinated according to the EPI schedule, and has not reported any complications following vaccination. There was no history of recurrent fractures or focal deficits.

On examination, the patient appeared irritable, with intense itching and continuous scratching over his entire body. He had a height of 86 cm and a weight of 11.8 kg, both below the 5th percentile. His temperature was 98°F, blood pressure was 90/60 mm Hg, pulse was 98 beats per minute, respiratory rate was 36 breaths per minute, and oxygen saturation was 100% on room air.

The patient had a prominent forehead, deep-set eyes, coarse facies, mild prognathism, dental caries, angular stomatitis, and a reddish-brown foul-smelling discharge from the right ear. Bilateral cervical lymph nodes were palpable, with the largest measuring 1.5 cm × 2.0 cm. Bilateral axillary lymph nodes were tender, measuring 2 cm × 2.5 cm, and the left inguinal lymph node was 1 cm in size. There were multiple healed scar marks on the body. He exhibited normal vesicular breathing with bilateral crepitations throughout the chest. The abdomen was soft, non-tender, with no visceromegaly. Cardiovascular and central nervous system examinations were unremarkable.

Based on history and examination, the patient was admitted with differentials of:

-Hyper IgE Syndrome.

-Chronic Granulomatous Disease.

-Leukocyte Adhesion Defect.

The following workup was planned to diagnose the patient: CBC with peripheral smear, Immunoglobin levels, flow cytometry, HIV screening, gene Xpert for stool and sputum was done to rule out Tuberculosis, liver function test, renal function test, chest X-RAY, ultrasound of swellings, HRCT of temporal bones and genetic analysis. Investigations are summarized in Table 1-3.

Radiological Evaluation

Dr. Ifra Tasawar (Radiology Department)

Chest X-ray showed peri-bronchial thickening most likely due to repeated chest infections (Figure 2A).

Wrist X-ray **s**howed significantly reduced bone density (Figure 2B).

Ultrasound of Swelling showed mild collection in bilateral axillae with cervical and axillary lymphadenopathy.

High-resolution computed tomography (HRCT) of temporal bones showed bilateral otitis media with mastoiditis.

NIH SCORE: 45

Diagnosis: Based on history, examination and investigations, a final diagnosis of HYPER IgE Syndrome (Jobs Syndrome) was made.

Management

The patient was managed with broad spectrum antibiotics, antifungal, nutritional rehabilitation and specialty consultations.

Antimicrobials

Broad spectrum including staphylococcal aureus coverage and antifungal, along with nutritional rehabilitation in the form of macronutrients, micronutrients and zinc supplementation.

Dermatological Consultation

Treatment of underlying dermatitis with superadded scabies was started.

Surgical Consultation

Abscesses were managed conservatively with no need of drainage.

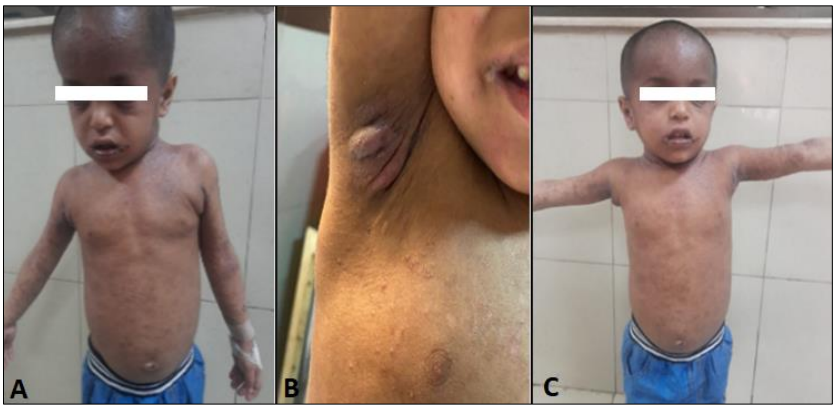

Figure 1: A) Picture showing multiple healed scar marks. B) Enlarged axillary Lymph nodes. C) Showing healed Scars and Anthropometry, showing weight and Height less than 5th Centile.

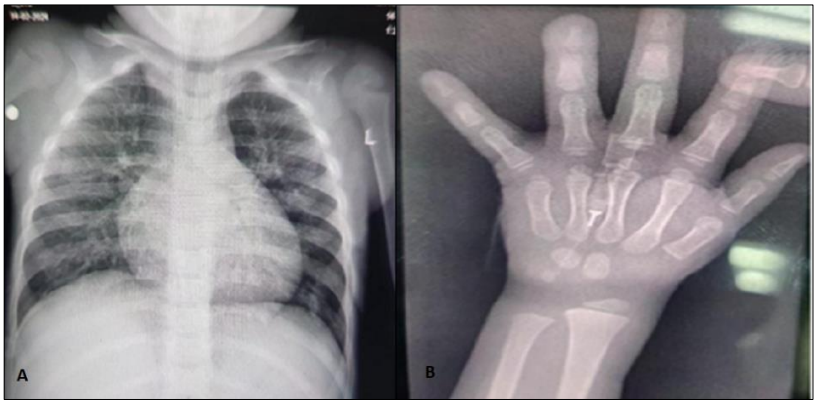

Figure 2: A) Peri-bronchial thickening most likely due to repeated chest infections. B) Significantly reduced bone density.

Table 1: Base line investigations

Investigation	Results		
		01.01.2023	**12.2.2024**
CBC	Hb	11.9g/dL	9.2g/dL
	HCT	36.4%	26.6%
	MCV	70.4fL	62.4fL
	TLC	45.41×10^3 /µl	12.4×10^3 /µl
	NEUTROPHILS	28%	47%
	LYMPHOCYTES	9%	22%
	EOSINOPHILS	57%	26%
	MONOCYTES	6%	5%
	PLATELETS	446×10^3 /µl	490×10^3 /µl
Ear swab c/s	Pseudomonas Aeruginosa	Serum, calcium, Phosphate, Alkaline phosphatase	NORMAL
HIV screening	Negative	LFTs and	NORMAL
GeneXpert	Negative	RFTs	NORMAL

Table 2: Serum Immunoglobin Levels

Serum IgA	Serum IgM	Serum IgG	Serum IgE
2.17 (0.2 -1 g/l)	0.74 (0.19-1.46 g/l)	16 (1.48 -6.31 g/l)	2400 (< 60 IU/ml)

Table 3: Flow cytometry

PARAMETERS	PATIENT VALUE	NORMAL RANGE
Absolute count of CD3+ total T-Lymphocytes	2883	1500-2900
Absolute count of CD4+ T-helper Lymphocytes	400	1000-2100
Absolute count of CD8+ T-regulatory Lymphocytes	2050	700-1100
Absolute count of CD19+ total B-Lymphocytes	560	500-1200
Absolute count of CD56+ Natural killer cells	245	300-600

Ent Consultation

Chronic suppurative otitis media was treated according to culture and sensitivity of ear swab.

Bmt Consultation

Decision about bone marrow transplantation is highly dependent on report of genetic testing which is awaited.

Discussion and Literature Review

Dr. Aisha Iftikhar: Hyper-IgE Syndrome constitutes a group of disorders classified under primary immune deficiency diseases. The classical triad includes atopic dermatitis, recurrent skin and lung infections, and elevated IgE levels. The estimated incidence is approximately 1 in 1,000,000, affecting both genders equally. It can manifest in autosomal dominant (AD), autosomal recessive (AR), and rare X-linked forms. Most cases of AD are sporadic due to de novo mutations. Navigating history can shed light on the landmark feats in discovery of the various clinical features that comprise this syndrome.

TABLE 4: NIH Scoring System (Depicted in table 4)

Clinical Findings	0	1	2	3	4	5	6	7	8	10
Highest IgE (IU/mL	<200	200-500			501-1000				1001-2000	#>2000
Total skin abscesses/boils	none		1-2		3-4				#>4	
Total pneumonias	none		1		2		3		#>3	
Parenchymal lung abnormalities	#none						Bronchi-ectasis		Pneuma-tocele	
Other serious infection	#none				present					
Fatal infection	#none				present					
Highest eosinophils/uL	<700			701-800			#>800			
Newborn Rash	#none				present					
Eczema (worst rash)	none	mild	Moderate		#severe					
Sinusitis/otitis (in worst year)	1-2	3	4-6		#>6					
Candidiasis	none	#Oral, vaginal	Finger nail		Systemic					
Retained primary teeth	#none	1	2		3				>3	
Scoliosis(Maximum curvature)	#<10		10-14		15-20				>20	
Minimal trauma fracture	#none				1-2				>2	
Hyperextensibility	#none				Present					
Characteristic face	none		#mild			Present				
Increased interalar distance	#<1 SD	1-2SD		>2SD						
High Palate	none		#present							
Congenital anomaly	#none					Present				
Lymphoma	#none				Present					

Findings in index patient are # marked. Our score is 45, > 15 score interprets high probability of HIES.SD-standard deviation.

Originally in 1966 Davis et al introduced it by reporting two girls with neonatal onset eczema, recurrent pulmonary and skin abscesses along with boils, naming it as JOB syndrome. Resemblance of this condition with that of the Biblical Prophet Job, characterized by sore boils, contributed to its nomenclature. [1]. Later in 1974 Buckley et al described two teenage boys having features of Job syndrome, but additionally dysmorphic features with exceptionally high IgE levels labelling as Buckley Syndrome [2].Hill et al., in 1974, declared that Job and Buckley syndromes are the same, naming it Hyper-IgE

Syndrome. Grimbecker et al., in 1999, characterized the autosomal dominant (AD) form as a multisystem disease due to its immune and non-immune manifestations affecting connective tissue, dental, and skeletal tissues. In 2004, Renner et al. identified additional features of increased susceptibility to cutaneous viral infections but noted the absence of connective tissue and skeletal features, terming this as the autosomal recessive (AR) form of Hyper-IgE Syndrome with combined immunodeficiency [3].Over the past two decades, genetic analysis has unveiled the underlying genetic causes. In the autosomal dominant (AD) form, heterozygous mutations in the signal transducer and activator of transcription-3 (STAT3) gene have been discovered. In the autosomal recessive (AR) form, biallelic mutations in the dedicator of cytokinesis-8 (DOCK8) gene have been identified. Additionally, other monogenic disorders with Hyper-IgE Syndrome-like phenotypes have been discovered, such as PGM3, ZNF431, and CARD11 [4].

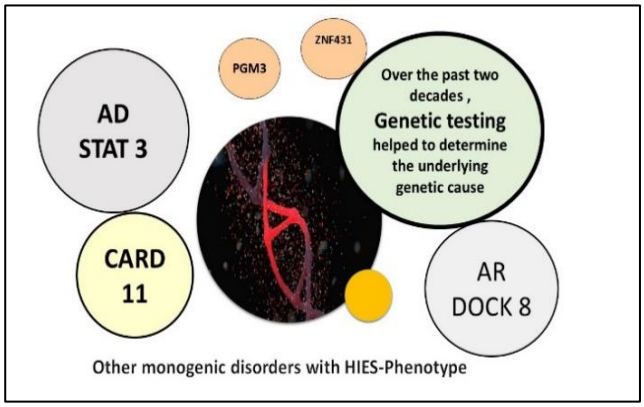

Figure 3: Various monogenic disorders with HIES-Phenotype

Clinical Features:

Hyper-IgE Syndrome (HIES) is a primary immune deficiency disorder attributed to genetic mutations.The classic autosomal dominant (AD) form of HIES can present with immunological manifestations, including recurrent cutaneous infections (e.g., Staphylococcal infections), recurrent pneumonia (e.g., Staphylococcus aureus, Aspergillus), and mucocutaneous candidiasis. Non-immunological manifestations include skeletal, dental, and connective tissue abnormalities. Characteristic facial features include a prominent forehead, deep-set eyes, facial asymmetry, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, and coarse facies. These features typically develop over time.

In the autosomal recessive (AR) form associated with DOCK8, eczema is a consistent feature. Patients are often truly atopic, developing allergies and asthma. In addition to sino-pulmonary and skin infections, there is a high susceptibility to viral infections.

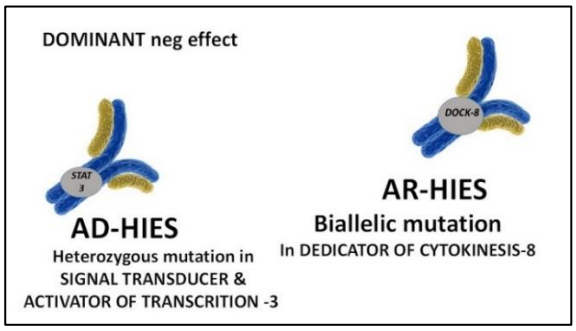

Figure 4: Mechanism of mutation and most important underlying genetic defects

Differentiating features of the AR (DOCK8) form from the AD (STAT3) form include central nervous system (CNS) manifestations, both infectious and non-infectious, such as vasculitis, vascular aneurysms, and brain infarcts. Notably, skeletal, dental, and connective tissue manifestations are absent in the AR form. The combination of pulmonary infections and impaired connective tissue remodeling in the AR form can lead to pneumatocele formation.

Pathogenesis

In AD form, heterozygous mutation in STAT3 gene impairs its function. STAT 3 is the transcription factor involved in signal

transduction of multiple cytokines including IL-6, IL-10, IL-11 and IL-21 (Fig.5A). IL-6 releases prostaglandin E and causes fever. It also affects T-Helper cells and early stages of follicular helper cells (Tfh) which in turn affects IL-17, IL-22 and Immunoglobulin class switching maturation respectively (Fig.5B). IL-17 and IL-22 have effects on keratinocytes & epithelial cells to produce chemokines and anti-microbial peptide which eliminate extra-cellular bacterial and fungal infections (Fig.5C).

IL-10 has anti-inflammatory and immunosuppressive effects, inhibiting the release of pro–inflammatory cytokines IL-1 and IL-6. STAT 3 has a crucial role in maintaining the balance between pro–inflammatory (IL- 6) and anti-inflammatory (IL-10) cytokines. (Fig 5 D)

B-cell differentiation is affected by IL-21. The level of IgE is suppressed by IL-10 and IL-21. STAT 3 also regulates timely teeth exfoliation and bone ossification through pleiotropic signaling. In the STAT 3 mutation all these functions are impaired explaining the underlying pathogenesis of clinical features.

In AR form, DOCK 8 regulates cytoskeletal re-arrangement which is important for cellular migration and Immune synapse formation. It is also important for proper T-Cell development, survival and function of CD8 T cell, NK cell activation and B cell activation (Memory cell) [5].

As a whole DOCK 8 has a broad range of effects on the immune system, leading to Immunodeficiency, autoimmunity and atopy [6].

Investigations

Marked elevation of Serum IgE (2000–100,000 IU /Ml) is considered the hallmark of disease. More than 90% of cases have eosinophilia (both these features do not co-relate with disease activity).

The rest of serum immunoglobulins are normal. Flow cytometry shows effect on T, B and NK Cells. Genetic mutational analysis is the gold standard.

Because of overlapping features with other conditions, NIH Scoring system was devised to assist the diagnosis, which includes presence and severity of clinical and lab findings. Total Score can help to clench diagnosis (0-15 unaffected, 16-39 possible, >40 diagnostic) [7]. (Table 4)

The use of genetic testing for diagnosis has a crucial role in determining therapeutic approaches [8].

In AR form (DOCK 8) besides eosinophilia and elevated IgE levels lymphopenia is also prominent. IgM level are low which may decline with age. IgG and IgA are usually normal.

Treatment

The therapeutic strategy for Hyper-IgE Syndrome (HIES) primarily focuses on the prevention and management of infections. Key components of treatment include preemptive skin care and prophylactic use of anti-staphylococcal and antimicrobial agents. Vigilance and early initiation of antimicrobials for skin and pulmonary infections are crucial measures [9]. Intravenous immunoglobulin (IVIG) replacement is reserved for patients with low levels of other serum immunoglobulin classes. The role of hematopoietic stem cell transplantation (HSCT) in the STAT3 form is currently being explored.

Treatment for the autosomal recessive (AR) form associated with DOCK8 is similar to that for the STAT3 form, but IVIG can also be beneficial. HSCT has a better prognosis for the AR form due to the exclusive impact of DOCK8 on the immune system. Live vaccines should be avoided. Antibody responses to vaccination are impaired to variable extent [10].

Differential Diagnosis

Most of the time the diagnosis is straightforward but often overlapping features with other phenotypically distinct PID conditions can raise suspicion e.g. CGD, LAD, Omenn Syndrome, Wiskot – Aldrich syndrome. Other conditions like Immune dysregulation, Atopic Dermitis, Hyper eosinophilic syndrome (HES) also need to be considered.

Chronic granulomatous disease (CGD)

These patients can also present with Skin abscesses, boils, repeated chest infections and recurrent fungal infections thus posing a challenge for the diagnosis. Important differentiating points are absence of eczema, and presence of hypergammaglobulinemia. Dihydrorhodamine (DHR) test can confirm the diagnosis.

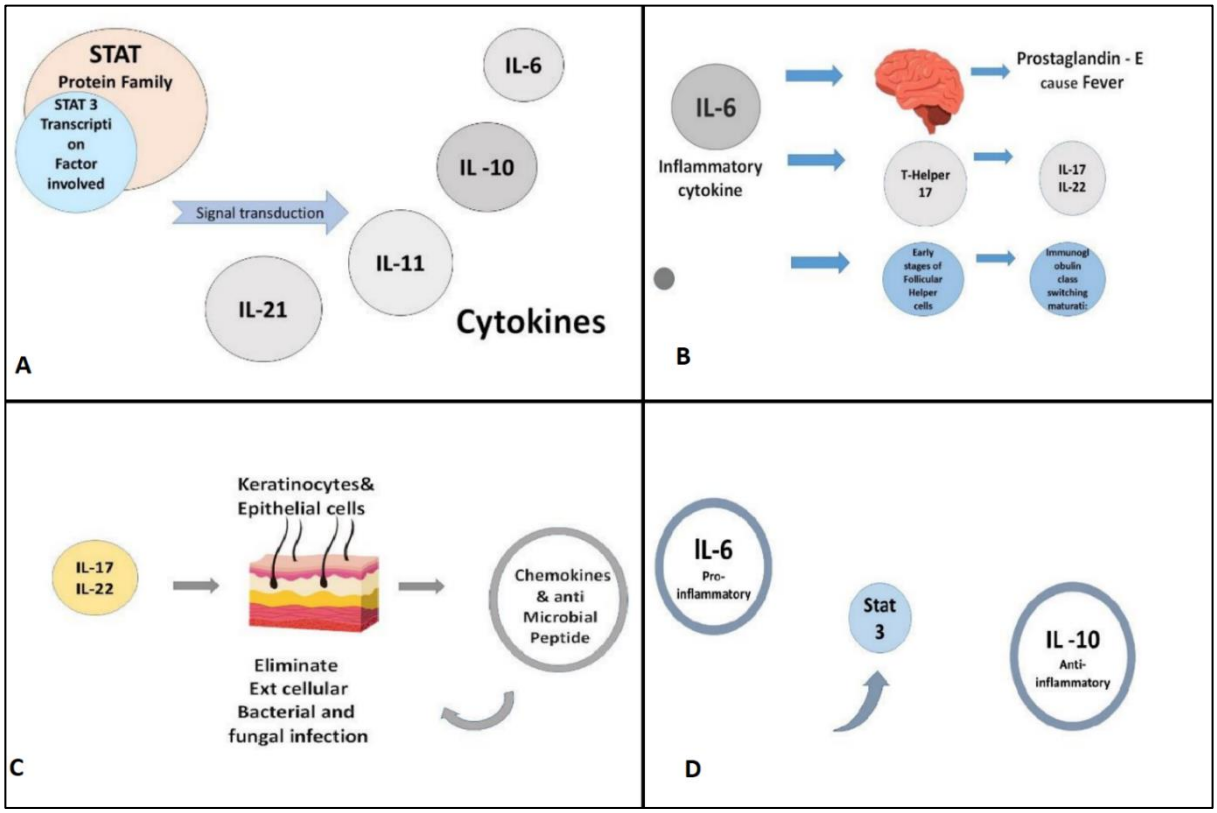

Figure 5: A) Role of cytokines in STAT 3 mutation), B (Multiple effects of IL 6),C (Antimicrobial effects of IL 17 and IL 22), D (Stat 3 required for balance between pro inflammatory (IL 6) and (IL 10) anti-inflammatory factors).

Leucocyte adhesion defect (LAD)

Patients with this condition present with recurrent abscesses particularly perianal and rectal regions, recurrent chest infection and oral thrush. Important points to consider in this entity is, absence of pus and H/O delayed umbilical cord shedding. Flow cytometry can help to confirm the diagnosis.

Omenn syndrome

In this condition there is oligoclonal proliferation of TH2 cell which infiltrates peripheral tissues and presents as eczema, erythroderma, diarrhea, FTT, mild eosinophilia, and elevated IgE level. Immunoglobulin level and flow cytometry can document the fundamental difference.

Atopic dermatitis (AD)

Skin manifestations of Hyper-IgE Syndrome (HIES) may resemble those of common atopic dermatitis both clinically and pathologically [11]. In atopic dermatitis, a defective skin barrier makes patients more susceptible to bacterial and

viral infections, and serum IgE levels are elevated. However, in atopic dermatitis, the immune system remains intact, and there are no deep abscesses or skeletal and connective tissue manifestations. The NIH Scoring System can help differentiate between the two conditions. In atopic dermatitis, serum IgE levels correlate with disease severity. In contrast, HIES is characterized by a long disease course from early life and an atypical distribution of skin lesions, including involvement of the axilla and groin, which are strong indicators of this condition [12].

Ipex syndrome

This rare condition is characterized by immune dysregulation, polyendocrinopathy, enteropathy, eczematous dermatitis. Most patients have mild eosinophilia and mildly raised IgE and IgA levels. T and B cells are normal and infection is generally not problem.

Hyper eosinophilic syndrome (HES)

This is also a very rare condition, mentioned here for theoretical purposes. The diagnostic criteria recommended by the International Cooperative Working Group on Eosinophil Disorders for Hyper eosinophilia Syndrome (HES) are very helpful. These criteria include: Blood eosinophilia of more than 1,500 eosinophils/µL on two separate examinations (at least one month apart, except in cases of life-threatening organ damage where diagnosis can be made immediately) and/or tissue eosinophilia; organ damage and/or dysfunction attributable to tissue eosinophilia; and exclusion of other disorders or conditions as the primary cause of organ damage [3}

Concluding Remarks

Prof. Javeed Iqbal: Hyper IgE Syndrome is a rare hereditary primary immunodeficiency. This case was selected because it is suitable for making residents aware of this entity. A special emphasis on salient clinical features and pathogenesis will enable them to identify this condition. Important differentiating points for close differentials have been added to enhance their ability of critical thinking, to facilitate an earlier diagnosis and thus lead to the timely institution of definitive therapy and prevention of complications.

Consent to Publication: Author(s) declared taking informed written consent for the publication of clinical photographs/material (if any used), from the legal guardian of the patient with an understanding that every effort will be made to conceal the identity of the patient, however it cannot be guaranteed.

Authors Contribution: Author(s) declared to fulfill authorship criteria as devised by ICMJE and approved the final version. The authorship declaration form, submitted by the author(s), is available with the editorial office.

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