DR SPUR'S MYSTERY CASE

A mystery case as old as time

Welcome to Dr Spur's Immunology Clinic
Referral letter:

UMPHONGOLO MEDICAL CLINIC

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Dear Dr Spur

I would appreciate your advice on a complicated patient. This is a 21-year-old female who has suffered from eczema since childhood. The eczema used to be very severe during childhood, but is presently more manageable with occasional flares. She currently has an axillary abscess, which is a painful, fluctuating mass under her left arm. She has had more than 20 abscesses over the past decade.

She has had multiple episodes of pneumonia since childhood (at least > 10 episodes) and had a left lower lobectomy at 18 months of age. She fractured her arm following minor trauma several years ago. She also suffers from recurrent episodes of Candida nail infections. She has had several teeth removed and has had recurrent dental infections.

She also said that some of her primary teeth did not erupt.

Laboratory investigations done
FBC: Significant eosinophilia (0.89 cells/uL)
Pus swab: Staph aureus, sensitive to methicillin
Elevated IgE levels: 8 676 kU/L
IgA, IgM, IgG: Normal

On allergy testing, she appears to be allergic to everything! Her allergen specific IgE levels were positive for all the inhalants and food tested.

Please advise on further investigation and management.

Kind regards
Dr Kagiso

Dear Dr Kagiso

Thank you for your kind referral. This is indeed a complicated case and she is definitely a candidate for further workup.

It is important to investigate her immune system, because she has suffered from several severe and recurrent infections. I always advise clinicians to think of me (Dr Spur) when they are dealing with a patient suffering from infections. Think **SPUR** – **S**evere, **P**ersistent, **U**nusual, **R**ecurrent infections. These should prompt clinicians to investigate the immune system further. They are important warning signs of a possible underlying immunodeficiency.

I requested baseline *Streptococcus pneumoniae* serotype-specific antibodies and subsequently vaccinated her with a polysaccharide vaccine, Pneumovax 23®. I repeated the *S pneumonia*e serotype-specific antibodies four weeks later. She responded with a two-fold increase to only three of the serotypes.

Her T- and B-cell lymphocyte sub-sets were normal, with normal lymphocyte proliferation to the recall antigen, Candida. Because she suffered from recurrent *S aureus* abscesses, I did the neutrophil oxidative burst, which was normal, but she demonstrated reduced neutrophil migration.

With such elevated IgE levels one should always consider the differential causes, including:

Atopic disease, eg Allergic diseases, Allergic Bronchopulmonary Aspergillosis (ABPA)

Parasitic infestation, eg Bilharzia and worms

Infectious diseases, eg TB, CMV, EBV, HIV

Inborn errors of immunity, eg Hyper-IgE syndrome, Wiskott Aldrich syndrome, immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), Omenn syndrome

Inflammatory diseases, eg Churg-Strauss (Eosinophilic granulomatosis)

Neoplasms, eg Lymphoma, IgE myeloma, etc

Liver disease.

Additional investigations done to exclude differential causes:

- Bilharzia serology: Negative
- Stool parasites: Negative
- Liver functions: Normal
- ANCA: Negative.

TABLE I: HYPER-IGE SYNDROME NIH SCORING SYSTEM

CLINICAL FINDINGS	POINTS*									
	0	1	2	3	4	5	6	7	8	10
Highest serum—IgE level (international units/mL)	< 200	200 to 500			501 to 1 000				1 001 to 2 000	> 2 000
Skin abscesses	None		1 to 2		3 to 4				> 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°		10 to 14°		15 to 20°				> 20°	
Fractures with minor trauma	None				1 to 2				> 2	
Highest eosinophil count (cells/microL)[A]	> 700			700 to 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 per year	1 to 2	3	4 to 6		> 6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyper extensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width[§]	< 2 SD	1 to 2		> 2 SD						
High palate	Absent		Present							
Young – age	> 5 years			2 to 5 years		1 to 2 years		≤ 1 year		

Owing to the apparent IgE sensitisation to all allergens tested on the Immunocap, I suspected non-specific IgE-binding due to the markedly elevated total IgE levels. This is a common phenomenon with very high total IgE levels and does not necessarily implicate true IgE-mediated allergy. I therefore requested an ISAC (Immuno-solid phase allergen chip) test. The ISAC test is a micro-array multiplex-specific IgE test that combines clinically relevant allergen components. Non-specific IgE-binding does not occur on the ISAC platform and the test is specifically indicated for patients who are multi-sensitised. In her case, the ISAC test was completely negative, confirming my suspicion of non-specific IgE-binding on the initial allergy tests.

An inborn error of immunity was strongly suspected due to a significant severe infection history, including Candida infections. The history of eczema, a fracture after minor trauma and the retention of primary teeth alluded to one of the syndromic inborn errors of immunity, and specifically Autosomal Dominant Hyper-IgE syndrome (AD-HIES) with a STAT-3 gene mutation. These patients often have low or low normal Th-17 cells. Your patient's T-helper 17 cells were low normal (0.4%). She also has a broad nasal bridge.

I used a Hyper-IgE NIH (National Institute of Health) scoring system developed by Grimbacher et al in 1999 (see Table I) as a guideline to help me make a diagnosis.

Diagnostic guidelines for Hyper IgE using the NIH scoring system:

- **Possible:** IgE > 1 000 U/mL, plus a score of > 30 on the five cardinal clinical features (recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic facies and high palate).
- **Probable:** The possible criteria met plus Th-17 cells are low to absent OR there is a family history of confirmed HIES.
- **Definitive:** The possible criteria plus a confirmed STAT-3 mutation.

A probable diagnosis of AD-HIES was made because she had an NIH score > 30 with low normal Th-17 cells. The diagnosis was subsequently confirmed with genetic testing. A pathogenic mutation was identified in STAT3. The STAT3 gene is associated with Autosomal Dominant STAT3 Hyper-IgE syndrome and Autosomal Dominant STAT3 gain-of-function.

Two forms of HIES have been described: autosomal dominant (AD) and autosomal recessive (AR) . These two forms share overlapping clinical and laboratory features, including eczema, recurrent infections, skin abscesses, high IgE level and increased eosinophil number.

AD-HIES, associated with heterozygous mutations in the transcription factor STAT3, is classified as an Inborn error of immunity, under the category Combined Immunodeficiencies with associated or syndromic features. It is also known as Job Syndrome.

Patients with AD-HIES may present with distinctive facial features (broad nasal bridge), bacterial infections (boils, pulmonary abscesses, pneumatoceles) due to *S aureus*, pulmonary aspergillus, *Pneumocystis jirovecii* pneumonia, eczema, mucocutaneous candidiasis, hyperextensible joints, osteoporosis and bone fractures, scoliosis, retained primary teeth and coronary and cerebral aneurysms.

Patients with AR-HIES due to DOCK8 mutation may be distinguished from those with AD-HIES by the occurrence of severe, recurrent viral infections caused by pathogens such as *Herpes simplex*, *Herpes zoster* and *Molluscum contagiosum*. There are other inborn errors of immunity that may also present with very high IgE levels.

The principal goals of the management of AD-HIES are aggressive treatment of infections and good skin care. As patients with HIES may lack the typical inflammatory features of infection, taking a good history, careful physical examination and appropriate imaging are necessary to pick up infections early.

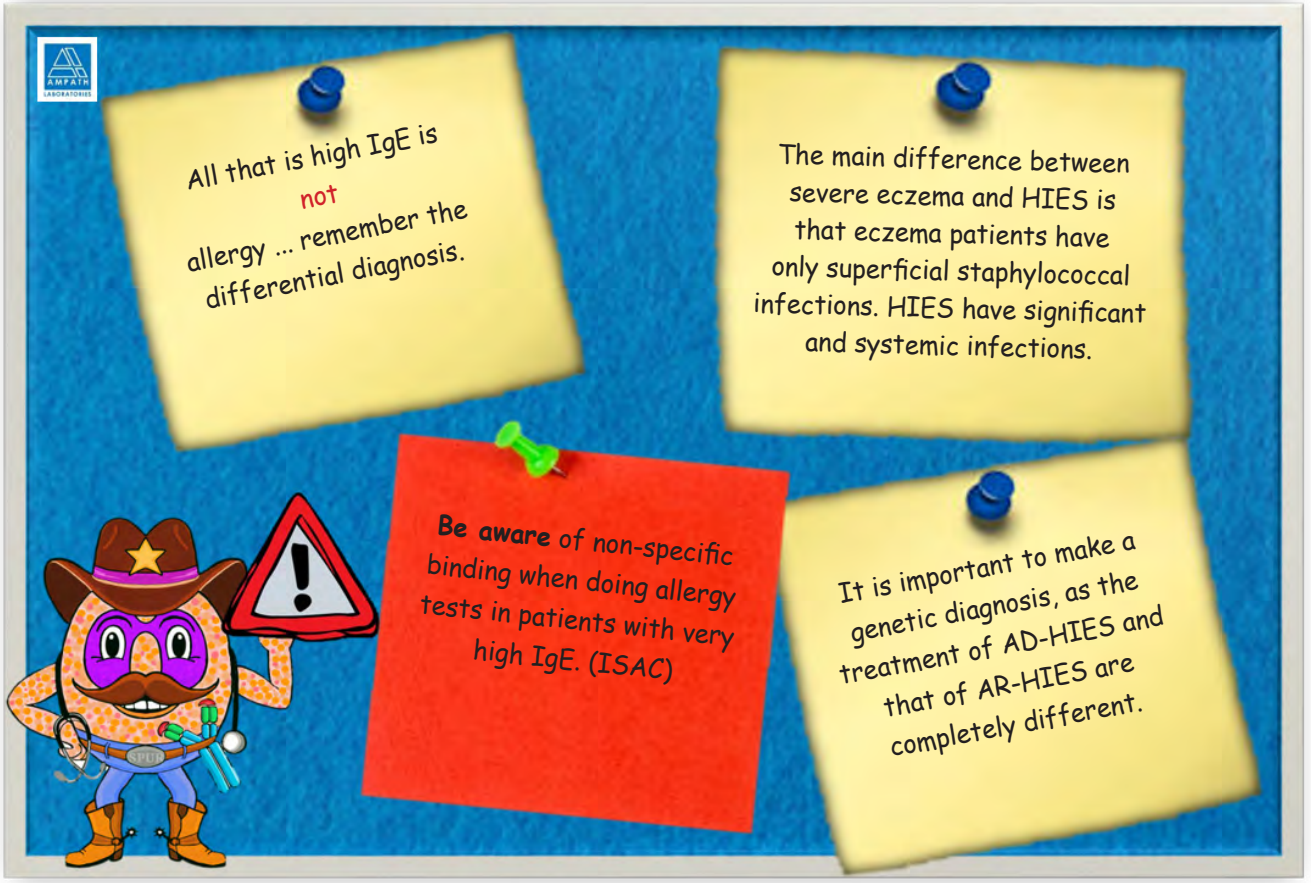
Treatment of the skin includes bleach baths or chlorhexidine washes and prophylactic antibiotics (eg, co-trimoxazole, which targets *S aureus*). Oral antifungal agents (eg, fluconazole) are generally effective in controlling the candidiasis, and, if necessary, they can be used as prophylaxis. Hypertension, if present, should be treated aggressively.

If vaccination responses are poor, it is reasonable to consider immunoglobulin replacement therapy in those who fail to respond. I therefore started your patient on IVIG, 600 mg/kg monthly.

Kind regards

Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

Diseases as old as time still occur … Read; the Book of Job, a case of Hyper-IgE syndrome

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