DR SPUR'S MYSTERY CASE

Allergy, atopic dermatitis, abnormal FBC and elevated IgE: what do you see?

Welcome to Dr Spur's Immunology Clinic
Referral letter:

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Dear Dr Spur

I have been seeing a four-year-old male patient for the past couple of months. He has presented since early childhood with recurrent respiratory tract infections with occasional episodes of acute gastroenteritis, bloody diarrhoea and severe atopic dermatitis. He was subsequently referred to a dermatologist, who did some laboratory investigations. These have indicated that he has elevated IgE levels of 1 204 IU/mL; the Phadiotop and an FX5 food-mix allergy screens were positive; however, the breakdowns have not been performed. A low platelet count of 30 × 10^9/L was noted on the full blood count (FBC).

This appears to be a complicated allergic patient with severe atopic dermatitis and an abnormal FBC. Could this perhaps be an inborn error of immunity? Any further guidance will be much appreciated.

Regards

Dr Glenda Hawkey

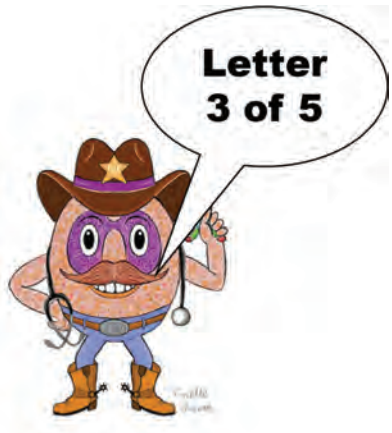
Dear Dr Hawkey

Thank you for the referral.

The patient presented with the triad of infections, low platelets and atopic dermatitis. This has raised the concern that we are dealing with a patient with an inborn error of immunity (IEI), most probably Wiskott-Aldrich syndrome (WAS). The differential diagnosis includes hyper-IgE syndrome, in particular DOCK8 deficiency, Omenn's syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, Comèl-Netherton syndrome and other combined immunodeficiencies.[1]

I conducted a baseline immune workup (refer to Table I) which included a full blood count (FBC) with differential count and platelet volume, immunoglobulins, specific antibodies, a lymphocyte immunophenotype and lymphocyte proliferation studies. These investigations were abnormal, with an elevated IgA, decreased IgM and persistently low CD4+, CD8+ T-cells, B and NK cells and low specific antibodies (antibodies to Tetanus toxoid and *Streptococcus pneumoniae* serotypes). The haematologist reported the absence of platelet clumping and reported that the platelets were small with a low mean platelet volume, indicating small-sized platelets.

I subsequently performed diagnostic vaccination to test T-cell-dependent and T-cell-independent antibody production pathways; he was vaccinated with tetanus toxoid and a pure polysaccharide pneumococcal vaccine (Pneumovax 23®) to test these pathways respectively. The specific antibodies were tested four weeks later and he had poor polysaccharide vaccine responses after vaccination with the pure polysaccharide vaccine (Pneumovax 23®); this indicated an abnormality in the T-cell-independent



pathway. He also demonstrated low class-switched memory B-cells and reduced lymphocyte proliferation studies to the recall antigens Tetanus and Varicella.

Owing to the presence of complex symptoms, poly-sensitisation and high levels of total serum IgE, I requested a multiplex IgE immunoassay. The patient demonstrated IgE sensitisation to the house-dust mite (HDM) components Der p 1, Der p 2, Der f 1 and Der f 2, Der p 10 (a tropomyosin), American cockroach tropomyosin, shrimp Pen m 1 (a tropomyosin), egg ovomucoid and Ara h3, a peanut storage protein.

The patient does not have a clinical history of any allergic symptoms after eating eggs, nuts or shellfish. It should be noted that patients with atopic dermatitis are often sensitised to multiple allergens due to a disrupted skin barrier. Sensitisation does not prove clinically relevant allergy and any positive allergen-specific IgE result should be correlated with the clinical history. A HDM allergy may aggravate atopic dermatitis and HDM avoidance measures should be practised. This patient has sensitisation to the tropomyosin component of HDM, which cross-reacts with tropomyosins found in muscle protein in arthropods (crustaceans, HDM, cockroaches) and molluscs. This may cause a clinically relevant shellfish allergy.

A probable diagnosis of Wiskott-Aldrich syndrome was made, which was subsequently confirmed with next-generation sequencing of an IEI genetic panel (see the ESID diagnostic criteria for WAS in Table II). A gene mutation was found in the X-linked gene WAS encoding for the WAS protein (WASp). The WAS protein is a cytoskeleton regulator which coordinates the pathways of actin filaments during cell signalling.[2] This impairs processes such as phagocytosis, immune synapse assemblement, and cell adhesion and migration.[2]

Spectrum of disease

Classically, Wiskott-Aldrich syndrome (WAS) (mode of inheritance: X-linked) presents with immunodeficiency, eczema and thrombocytopaenia with small platelets.[4] Certain criteria need to be met to diagnose WAS (refer to Table II). Patients may develop severe eczema, bleeding tendencies such as prolonged or spontaneous bleeding, bruising, petechiae and bloody diarrhoea in the first years of life.[2,4] They also suffer from recurrent infections such as bacterial respiratory infections and chronic viral infections (herpes viruses, molluscum contagiosum and papilloma viruses).[4]

Congenital thrombocytopaenia with small platelets is a diagnostic hallmark of Wiskott-Aldrich syndrome. Many patients have increased IgE and IgA levels, with low IgM levels and poor polysaccharide vaccine antibodies after vaccination or a natural infection. T-cell numbers and function decline with age.

A Wiskott-Aldrich syndrome patient has an increased risk of an autoimmune disease such as haemolytic anaemia, IgA nephropathy, inflammatory bowel disease (IBD) and arthritis.[4] Furthermore, patients may develop Epstein-Barr virus (EBV), induced lymphoproliferative disease, leukaemia and lymphoma.[4]

Supportive treatment in these patients includes antimicrobial prophylaxis and immunoglobulin replacement therapy while curative treatment is undergoing a haematopoietic stem-cell transplant (HSCT) or targeted gene therapy.[2,4] A bone marrow transplant is preferably done within two years of age and has demonstrated a 97% survival rate internationally in these patients.[2] Targeted gene therapy is available only with those WAS patients who cannot find a fully matched donor.[2] The most recent trials have demonstrated some good success with the resolution of symptoms, but this treatment option is not yet available in South Africa.[2]

Occasionally, patients have moderate thrombocytopaenia (platelets of 50–100 × 10^9/L) and no other significant findings. X-linked thrombocytopaenia (XLT) is a muted form of WAS due to a missense mutation.[4,5] Patients suffering from XLT may present with thrombocytopaenia, mild to moderate infections and absent or mild eczema.[5] Treatment is often debatable as there are no clear guidelines, but it may range from splenectomy or a bone marrow transplant, to more conservative approaches such as the avoidance of contact sports and wearing a helmet.[5] More invasive procedures necessitate many aspects to be factored in before a decision is taken, owing to complications.[5]

In the world of allergies and inborn errors of immunity (IEI), the clinical presentation may be on a spectrum and may be variable. Unfortunately, IEIs are already underreported and often undiagnosed in South Africa.[6] IEIs occur due to monogenic mutations that control immunoregulation and immune host defences.[4] The major phenotypes of IEIs include recurrent infections, inflammatory disease, autoimmunity, lymphoproliferation and malignancy.[4,7] Allergic manifestations include food allergy, eczema, allergic rhinitis (AR) and asthma.[4]

Allergic disease may be the initial manifestation of an underlying IEI, which furthermore contributes to either a delayed diagnosis or misdiagnosis.[4,8] The general practitioner should be aware of IEIs, the ways in which they present, which investigations to initiate and when to refer them to a specialist. Patients with IEI often present at the general practitioner first with a combination of non-specific symptoms, including allergic manifestations, problematic infections and autoimmunity. A high index of suspicion and early investigations with a correct and early diagnosis will prevent end-organ damage and improve the patient's quality of life (QoL) with the application of targeted therapies.[4]

TABLE I: LABORATORY INVESTIGATIONS			
Test	**Ranges**	**2023-01-20**	**2023-02-17**
Haemoglobin	11.0–14.0 g/dL	12	12.7
Red cell count	4.00–5.20 10^12/L	4.82	4.58
Haematocrit	34.0–40.0%	37.8	36
MCV	75.0–87.0 fl	78	78.7
MCH	24.0–30.0 pg	25.4	28.5
MCHC	31.0–36.0 g/dL	33.2	33.5
RDW	11.8–14.6%	12.5	13.2
White cell count	5.00–15.00 10^9/L	5,95	5,01
Neutrophils Absolute count (Abs)	1.50–8.00 10^9 L	2.00	1.45 L
Lymphocytes Abs	6.00–9.00 10^9/L	2.02 L	2.04 L
Monocytes Abs	0.20–1.00 10^9L	0.80	0.78
Eosinophils Abs	0.00–1.00 10^9/L	1.00	0.90
Basophils Abs	0.00–0.10 10^9L	0.10	0.10
Platelet count	137–373 10^9/L	30 L	32 L
Mean platelet volume (MPV-H)	7.1–11.0 fl	4 L	4 L
ESR	0–13 mm/hr	11	8
CD45 Lymphocytes	1 400–5 500 cells/uL	1 506	
Total T-cell Abs	1 400–3 700 cells/uL	1 025 L	
CD4 cells Abs	700–2 200 cells/uL	645 L	
CD8 cells Abs	490–1 300 cells/uL	380 L	
Tot B cells Abs	390–1 400 cells/uL	280 L	
Tot NK cells Abs	130–720 cells/uL	110 L	
IgA	0.50–1.92 g/L	2.03 H	2.15 H
IgM	0.43–1.66 g/L	0.35L	0.37 L
IgG	4.85–13.18 g/L	8.98	
IgG 1	3.62–12.28 g/L	5.75	
IgG 2	0.57–2.90 g/L	2.90	
IgG 3	0.129–0.789 g/L	0.447	
IgG 4	0.013–1.446 g/L	0.354	
IgE	0.0–40.0 IU/mL	1 350 H	
Tetanus IgG	> 0.10 IU/mL	0.06 L	1.20
S pneumoniae type 1 IgG	> 1.30 ug/mL	0.07 L	0.10 L
S pneumoniae type 3 IgG	> 1.30 ug/mL	0.30 L	0.45 L
S pneumoniae type 4 IgG	> 1.30 ug/mL	0.24 L	0.35 L
S pneumoniae type 5 IgG	> 1.30 ug/mL	0.25 L	0.47 L
S pneumoniae type 6A IgG	> 1.30 ug/mL	0.99 L	1.54
S pneumoniae type 6B IgG	> 1.30 ug/mL	0.46 L	0.88 L
S pneumoniae type 7F IgG	> 1.30 ug/mL	0.48 L	0.74 L
S pneumoniae type 9V IgG	> 1.30 ug/mL	1.50	2.05
S pneumoniae type 14 IgG	> 1.30 ug/mL	0.29 L	0.55 L
S pneumoniae type 18 C IgG	> 1.30 ug/mL	0.60 L	0.89 L
S pneumoniae type 19A IgG	> 1.30 ug/mL	0.96 L	1.25 L
S pneumoniae type 19F IgG	> 1.30 ug/mL	1.19 L	1.20 L
S pneumoniae type 23 IgG	> 1.30 ug/mL	1.15 L	2.89
Pneumococcal percentage	%	8	23
Lymphocyte proliferation to PWM	> 10 SI	20	25
Lymphocyte proliferation to Tetanus	> 3 SI	1.5 L	1.3 L
Lymphocyte proliferation to Varicella	> 3 SI	2.5 L	2.7 L
Lymphocyte proliferation to Candida	> 3 SI	5	4.8

TABLE II: ESID DIAGNOSTIC CRITERIA FOR WAS[3]

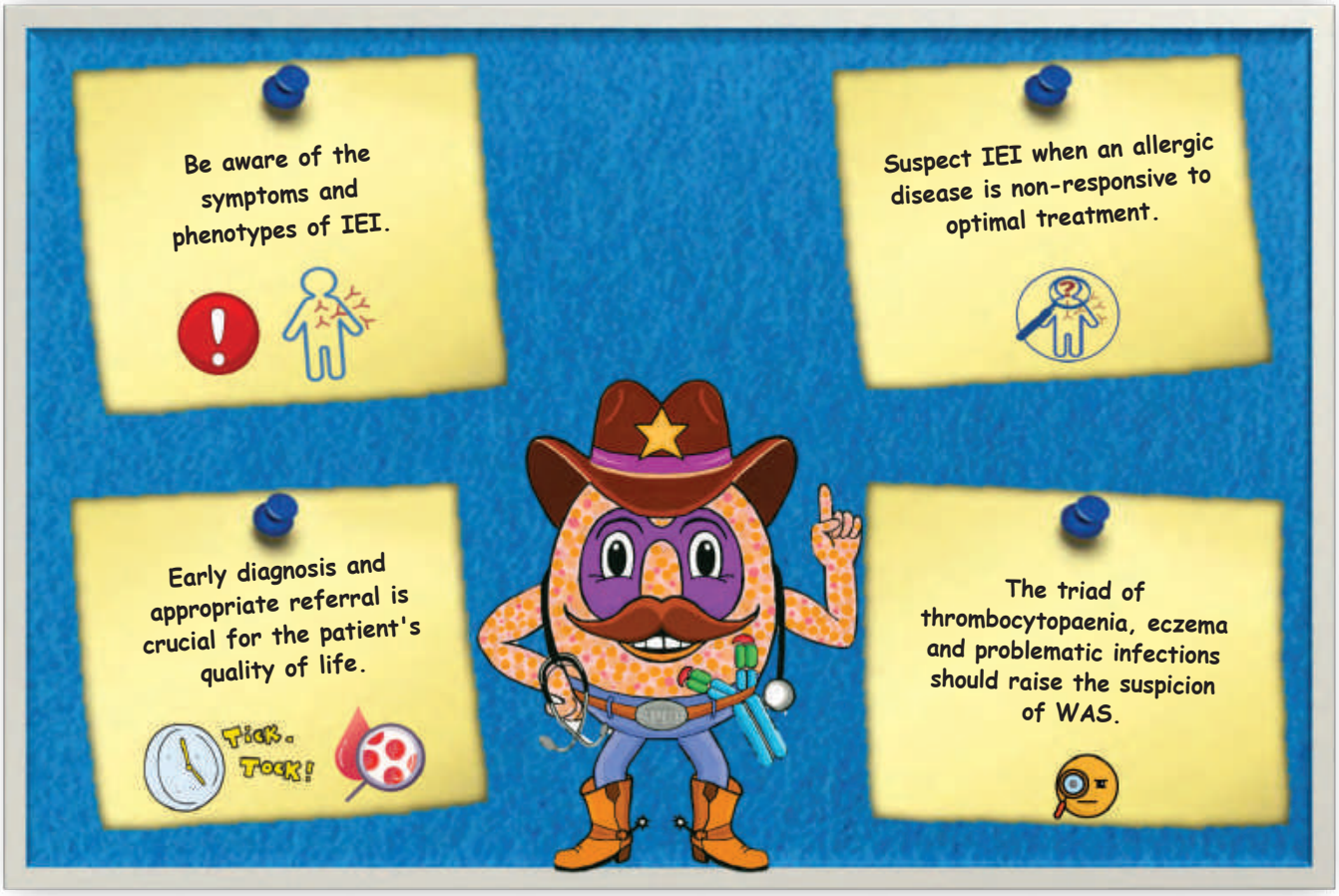
Definitive	Probable	Possible
Male patient with congenital thrombocytopaenia (platelets less than 70 × 10^9/L), small platelets and at least one of the following:	Male patient with congenital thrombocytopaenia (platelets less than 70 × 10^9/L), small platelets and at least one of the following:	Male patient with thrombocytopaenia (platelets less than 70 × 10^9/L) and small platelets; or a male patient splenectomised for the thrombocytopaenia who has at least one of the following:
1. Mutation in WASP 2. Absent WASP mRNA on northern blot analysis of lymphocytes 3. Absent WASP protein in lymphocytes 4. Maternal cousins, uncles or nephews with small platelets and thrombocytopaenia	1. Eczema 2. Abnormal antibody response to polysaccharide antigens 3. *Recurrent bacterial or viral infections* 4. Autoimmune diseases 5. Lymphoma, leukaemia or brain tumour	1. Eczema 2. Abnormal antibody response to polysaccharide antigens 3. *Recurrent bacterial or viral infections* 4. Autoimmune diseases 5. Lymphoma, leukaemia or brain tumour

Some diagnostic clues may aid in the diagnosis of an underlying IEI that presents with allergic disease:[1,7]

1. Severe allergic disease that has poor or no response to treatment.[7]
2. Early-onset allergic disease such as a eczematous skin lesion appearing before two months of life.[1]
3. A positive family history of IEI.[7]
4. A family history of severe atopy or other immunological disorders.[7]

If uncertainty exists, referral to a specialist is appropriate. Ultimately, the QoL and the survivability of these patients depends on us; therefore, clinicians should have a high index of suspicion for an underlying IEI.

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

when the real clue is in the FBC and not the IgE, a case of Wiskott-Aldrich syndrome is most probable.

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