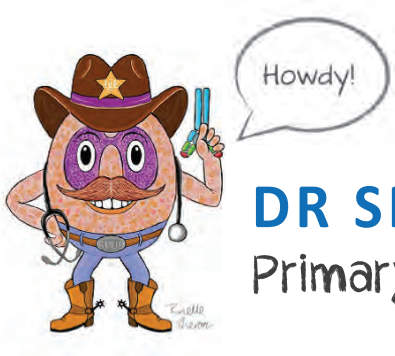


DR SPUR'S MYSTERY CASE

Primary immunodeficiency disorders

Welcome to Dr Spur's Immunology Clinic Referral letter:

Morningside

General Practice

Health for Life

Dear Dr Spur

Mrs Thumi Monatheng is a 63-year-old lady known in my practice for 15 years. She has Hashimoto's disease with hypothyroidism, alopecia areata with temporal hair loss and hypertension. She persistently has a low-positive speckled antinuclear antibody with joint pains in her thumbs. She suffers from seasonal allergic rhinitis (AR), is sensitised to grasses and has reactive airways. She has consulted a rheumatologist, an endocrinologist, a cardiologist and a pulmonologist and she is on optimal treatment for the abovementioned conditions. Her current treatment comprises Dazit one tablet twice daily, Coveram 10/5 one tablet daily, Euthyrox 100 +12.5 mg daily, Relvar Ellipta 92/22 inhalations daily and Celebrex 200 mg daily. She suffered from a severe case of Herpes Zoster after a dental procedure that took weeks to clear.

The reason why I am consulting you is that she has persistently low IgM levels of <0.2 g/L (0.4–2.3) with normal levels of IgG and IgA on three separate occasions when she was not ill. She has a history of two episodes of laryngitis with and/or without bronchitis and has two severe episodes of sinusitis every year that only resolve on antibiotic treatment. It was always assumed that these episodes are secondary to her AR, but your opinion on this will be valued. Do we need to be concerned about her low IgM levels?

Thank you for seeing this patient.

Kind regards

Dr Rachel Mohlape

Dear Dr Mohlape

Thank you for your referral of Mrs Monatheng. From her history, she clearly has immune dysregulation with a significant infection history, autoimmunity and allergies. A comprehensive investigation of her humoral and cellular immune system was done. Secondary causes of immunodeficiency should always be excluded. The serum protein electrophoresis was normal with no protein loss in her urine or stool. No malignancies were detected.

She did not respond to Pneumovax 23® vaccination (pure polysaccharide vaccine) at all. At baseline, she had a protective antibody response to only 8% of *S. pneumoniae* serotypes. Six weeks after vaccination, she showed no increase in specific antibody responses to *S. pneumoniae* serotypes. A protective response to at least 70% of tested *S. pneumoniae* serotype-specific antibodies is regarded as a sufficient or normal response. However, she responded normally to Tetanus and Diphteria toxoid vaccines. She therefore has a T-cell independent antibody non-responsiveness due to her lack of response to the polysaccharide vaccine. A diagnosis of selective IgM deficiency was made and she was started on prophylactic Azithromycin therapy.

Selective IgM deficiency (SIGMD) is defined as IgM levels <2 SD of normal on two separate occasions (usually <0.30 g/L in adults and <0.20 g/L in children) with normal levels of IgA and IgG with recurrent infections that are often severe. It was largely ignored as an immunodeficiency and has only recently (since 2017) been included in the International Union of Immunological Societies' (IUIS) classification of Primary Immunodeficiency Diseases (PID) and 2019 IUIS classification of Inborn Errors of Immunity. SIGMD appears to be more common than initially thought. A prevalence of 0.07–2.1% in immunology and immunodeficiency clinics has been reported. SIGMD occurs in adults and children, but can be a transient finding in children.

Selective IgM deficiency is likely a heterogeneous disorder. Infections are the most common clinical presentation. Secondary causes for decreased IgM levels, including malignancies, should always be excluded. Approximately 80% of patients present with recurrent infections to common microbes. The infectious presentations of SIGMD include recurrent otitis media, chronic sinusitis, bronchitis, bronchiectasis, pneumonia, urinary tract infections, cellulitis and even meningitis and sepsis. Microbial organisms implicated include *Streptococcus pneumoniae, Hemophilus influenzae, Neisseria meningitidis, Pseudomonas aeruginosa, Aspergillus fumigatus* and *Giardia lamblia*. Widespread Molluscum contagiosum has also been reported.

Allergic diseases are the second most common presentation of SIGMD and up to 40% of these patients may present with

an allergic disorder. There is an increased prevalence of autoimmune diseases, which in both human beings and mice appear to be secondary to selective IgM deficiency rather than IgM deficiency secondary to autoimmune diseases. Autoimmune diseases reported in patients with SIGMD include Hashimoto's disease, systemic lupus erythematosus, vitiligo, Sjogren's syndrome, rheumatoid arthritis, Coeliac's disease, Crohn's disease, autoimmune cytopaenias, Addison's disease and autoimmune glomerulonephritis.

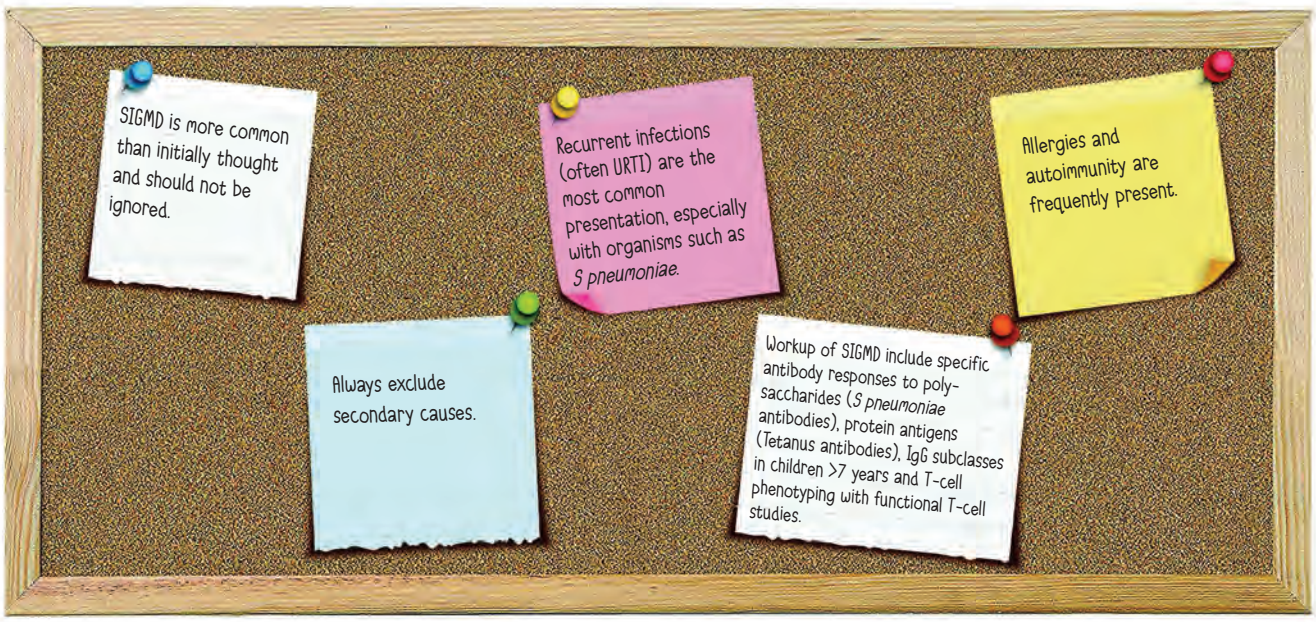
Specific IgG antibody responses against *S pneumoniae* polysaccharides are impaired in a subset of patients with selective IgM deficiency. IgG subclass deficiency has been reported in few cases of SIGMD and this is analogous to the association with selective IgA deficiency and an IgG subclass deficiency. T-cell numbers and functions are intact.

Management includes prophylactic antibiotics and prompt treatment of febrile illness. Symptomatic SIGMD patients with specific antibody deficiency may be considered candidates for immunoglobulin treatment, especially if prophylactic antibiotics fail.

Thank you for the referral.

Kind regards
Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

'A case of an ignored, underestimated immunodeficiency: Selective IgM Deficiency'

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