DR SPUR'S MYSTERY CASE

Primary immunodeficiency disorders

Referral letter:

Haematology Clinic
Dr Adams
Clinical Haematologist

Dear Dr Spur,
Thank you for seeing this challenging patient of mine;

Mr Will is a 65 year old man who has been attending my haematology clinic for 2 months, with a diagnosis of Evans syndrome.

He initially presented to the emergency department with progressive malaise and yellowing of his sclera. On examination it was found that he was markedly pale, had petechiae on the lower legs and trunk and was jaundiced. No organomegaly or lymphadenopathy was found.

Bloodwork was ordered and his full and differential blood count showed a macrocytic anaemia and severe thrombocytopenia. The peripheral smear showed evidence of haemolysis, including polychromasia, spherocytes and nucleated red cells. His infective workup was negative.
The liver function tests showed raised total bilirubin with the unconjugated fraction increased and slightly elevated LDH. A haemolytic screen revealed a positive direct Coombs, suggesting immune mediated haemolytic anaemia.

After extensive investigations for the causes of autoimmune haemolytic anaemia and thrombocytopenia, which included autoimmune screens, an infective work up, excluding malignancy and medication use, Mr Will was diagnosed with Evans syndrome – autoimmune haemolytic anaemia and primary idiopathic thrombocytopenia. He was started on high doses of glucocorticosteroids and referred to my clinic for follow-ups.

Unfortunately Mr Will is not responding to the glucocorticosteroid therapy and presented with gradually worsening cytopenias. In addition, Mr Will complained of fever, coughing and chest pain. I diagnosed him with severe pneumonia and admitted him to hospital for intravenous antibiotics. After recovering he had a subsequent severe haemolytic crisis, for which I admitted him to ICU. He developed another episode of pneumonia two months later which was thought to be secondary to the high dose glucocorticosteroid therapy.

I suspect that there is something more to Mr Will's medical condition, perhaps an underlying immunodeficiency? Can you kindly assist me with further investigations and suggested management?
Kind regards

Dr Adams

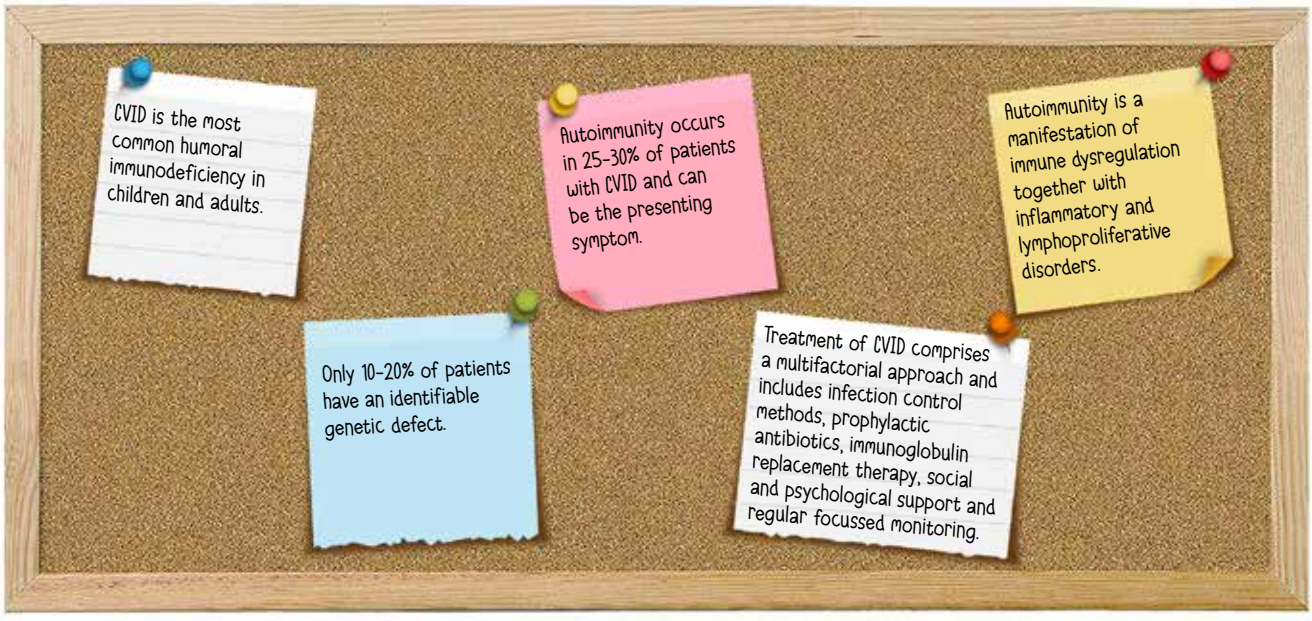
Welcome to Dr Spur's Immunology Clinic

Dr Spur took a thorough personal and family history from Mr Will and noted that he had no previous history of recurrent or atypical infections as a child or in early adulthood. There is also no significant family or medical history of note prior to his diagnosis of Evans syndrome.

Dr Spur started his investigations with baseline serum immunoglobulins, and found severely decreased IgG, IgM and IgA levels. Further immunological tests included specific antibodies against recall antigens, namely, Tetanus toxoid, Diphtheria toxoid, *S pneumoniae* and *H influenza*, which were all markedly decreased. Memory B-cells were decreased and an immunophenotype of the lymphocyte subsets showed a mild decrease in B-cell numbers. Mr Will was revaccinated against the recall antigens with a vaccine containing the protein antigens Tetanus and Diphtheria toxoids and a polysaccharide vaccine containing 23 *S pneumoniae* serotypes in order to test T cell-dependent and T cell-independent vaccine responsiveness respectively. The vaccine responses were tested four weeks later, with a suboptimal response noted to the protein antigens (Tetanus and Diphtheria Toxoids) and polysaccharide antigens (*S pneumoniae*). Serum immunoglobulin levels were also repeated and were still markedly low.

Dr Spur made the diagnosis of common variable immune deficiency (CVID), initially presenting with autoimmune cytopaenias. Mr Will was immediately started on intravenous immunoglobulin replacement therapy (IVIG) together with his immunosuppressive medication for the cytopaenias. This combination not only increased his IgG levels but also improved his haemoglobin and platelet count. Dr Spur advised Mr Will that he would need IVIG 3–4 weekly together with close immunological and haematological monitoring.

Dr Spur's take-home message:



At least one of the following:
- Increased susceptibility to infection
- Autoimmune manifestations
- Granulomatous disease
- Unexplained polyclonal lymphoproliferation
- Affected family member with antibody deficiency

AND

- Marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age)

AND

At least one of the following:
- Poor antibody response to vaccines (and/or absent isohaemagglutinins);
- Absence of protective levels despite vaccination where defined
- Low-class-switched memory B-cells (<70% of age-related normal value)

AND

- Secondary causes of hypogammaglobulinaemia have been excluded (eg infection, protein loss, medication, malignancy)

AND

- Diagnosis is established after the 4th year of life (but symptoms may be present before)

AND

- No evidence of profound T-cell deficiency, defined as 2 out of the following (y = years of life):
- CD4 numbers/microlitre: 2–6y <300, 6-12 y <250, >12 y <200
- % naive of CD4: 2–6 y <25%, 6–16 y <20%, >16 y <10% T-cell proliferation absent

Dr Spur's mystery SOLVED: "An unexpected case of CVID"

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