DR SPUR'S MYSTERY CASE

Connecting the dots in IEI: infections and tumours

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr Peter Evans
SPECIALIST PHYSICIAN

Dear Dr Spur

I am seeing a 25-year-old female patient who has a history of frequent respiratory infections since adolescence. She had an uneventful childhood, but started getting infections of increasing frequency and severity during her adolescence, to the point where she required several antibiotic prescriptions per year, and hospital admission at least twice a year for pneumonia. She had chronic productive cough between pneumonia episodes, with features of early bronchiectasis. We diagnosed common variable immunodeficiency (CVID) and prescribed a prophylactic antibiotic. The patient is not using corticosteroids, immunosuppressant medications or anticonvulsants. She receives 75 mcg of L-thyroxine daily for hypothyroidism. While she reports no family members with frequent or atypical infections, there is a history of thyroid disease, inflammatory bowel disease (IBD), leukaemia and gastric cancer affecting several relatives.

I saw her again this week, and she reports only minor upper respiratory infections over the past six months. There are no signs of anaemia, jaundice, oedema, clubbing or lymphadenopathy. However, I palpated an enlarged spleen and sonographic investigation confirmed splenomegaly with an estimated spleen size of 18 cm × 15 cm. I ordered a thoracoabdominopelvic CT scan which excluded hepatobiliary disease and lymphadenopathy. A sonar-guided splenic biopsy revealed diffuse large B-cell lymphoma (DLBCL).

It appears to me that several immune system processes are simultaneously compromised in different members of this family including infection immunity, immunological tolerance and anti-tumour immunity. Is this new cancer diagnosis linked to the patient's known CVID diagnosis? If so, how should we adjust our follow-up care plan for this patient in future? Your guidance is appreciated.

Kind regards
Dr Peter Evans

Dear Dr Evans

Thank you for the consultation. CVID is one of the most common inborn errors of immunity (IEI) encountered in practice, and these patients get infections, as well as non-infectious comorbidities like allergic disease, autoimmunity, lymphoproliferation and malignancies.[2]

The diagnosis of CVID is based on evidence of frequent sinopulmonary infections, reduced serum levels of IgG and IgA, with or without reduced levels of IgM, reduced B-cell or memory B-cell numbers, and suppressed vaccine responses.[1] The diagnostic criteria for CVID are summarised in Table I. CVID patients may also develop non-infectious manifestations such as allergic disease, autoimmunity, lymphoproliferation and malignancies.[2] The highest frequency of infectious and non-infectious complications occur in patients with < 2% class-switched memory B-cells.[3] An example of a patient report showing some of the typical immunological findings in CVID is given in Table II. Please note the decreased immunoglobulin levels including very low IgE, reduced memory B-cells, poor vaccine response to pneumococcal polysaccharide and reduced T-cell function.

Splenomegaly is an important clinical finding in any patient with IEI. The spleen is a major lymphoid organ, and an important site for B-lymphocyte development. Immature B-cells leave the bone marrow and settle in the germinal centres of splenic lymphoid follicles where they are exposed to self and foreign antigens by mature T-follicular helper (Tfh)-cells.[3] This interaction induces somatic hypermutation and class-switching of immunoglobulin genes that expands the B-cell antibody repertoire, and increases antibody affinity and specificity.[3]

T-cell dysfunction can manifest clinically as opportunistic infections (*Pneumocystis jiroveci*, *Cryptosporidium parvum*, systemic fungal infection, severe herpes viral infection) or autoimmune disease. T-cell dysfunction is shown in the laboratory by testing lymphocyte proliferation to recall antigens. T-lymphocytes are important for the killing of viruses, bacteria, fungi, protozoa, parasites, infected cells and cancer cells. Their other essential roles include supporting specific antibody production by B-cells, and inducing immune tolerance in immature B- and T-cells (Tregulatory cells or T-regs).[4] T-cells develop in the thymus and migrate to the secondary lymphoid tissues as naive T-cells. There they are exposed to self and foreign antigens by antigen-presenting B-cells, and induced to mature into different T-lymphocyte subclasses such as CD4+ T-cells, CD8+ Tcells, regulatory T-cells (T-regs), T-follicular helper cells, memory T-cells, etc.[4] Alterations in Tlymphocyte number and function have been described in some CVID patients, but are not universally present.[5] Profound T-cell defects are more likely to represent a combined immunodeficiency disorder rather than CVID.

While the pathophysiology of CVID is incompletely understood, 10% of patients have monogenic defects.[5] CVID-associated genetic mutations frequently affect B-cell development.[6,7] Since antigen-presenting B-cells provide developmental support to naïve T-cells in secondary lymphoid tissues, mutations affecting B-cell function may also indirectly affect T-cell function.[6] In turn, T-follicular helper cells support B-cell maturation in the spleen, whereas regulatory T-cells (T-regs) induce immune tolerance in B-cells. Mutations affecting T-cell differentiation may indirectly impair B-cell function.[6,7] Furthermore, reduced T-regs as a result of defective T-cell differentiation may cause autoimmunity and immune dysregulation.

The IEI spectrum is complex because of the number of role-players and many layers of cellular communication involved

TABLE I: ESID CRITERIA FOR THE DIAGNOSIS OF CVID[1]

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 isohemagglutinins); that is, the absence of protective levels despite vaccination where defined Low 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 fourth year of life (although symptoms may be present earlier)
AND no evidence of profound T-cell deficiency, defined as two of the following: CD4 cells/μL: 2–6 years < 300, 6–12 years < 250, > 12 years < 200 % naive CD4: 2–6 years < 25%, 6–16 years < 20%, > 16 years < 10% T-cell proliferation absent

TABLE II: PATIENT REPORT SHOWING SOME OF THE TYPICAL IMMUNOLOGICAL FINDINGS IN CVID PATIENTS

Laboratory investigation	Baseline result	Result after six weeks	Reference range
IgA	**0.45**		0.70–4.00 g/L
IgM	**0.38**		0.40–2.30 g/L
IgG	**4.2**		7.00–16.00 g/L
IgE	**< 2.0**		0.0–100.0 IU/mL
Total lymphocytes	2 177		1 400–12 100 cells/ul
Total T-lymphocytes Absolute	1 899		690–2 540 cells/ul
CD4+ Lymphocytes Absolute	710		358–1 259 cells/ul
CD8+ Lymphocytes Absolute	799		194–836 cells/ul
Total B-lymphocytes Absolute	278		90–660 cells/ul
Total NK cells Absolute	120		90–590 cells/ul
CD27+ IgD- class-switched B-cells	**2.8**		7.2–12.7%
CD27+ IgD+ non-switched B-cells	**4.5**		7.4–13.9%
Lymphocyte proliferation to tetanus	12		Stimulation index > 3
Lymphocyte proliferation to varicella	**1**		Stimulation index > 3
Lymphocyte proliferation to candida	**2**		Stimulation index > 3
Tetanus IgG	<0.01	0.90	> 0.1 IU/mL
S. Pneumoniae serotype 1 IgG	0.86	**2.16 #**	> 1.3 ug/mL
S. Pneumoniae serotype 3 IgG	0.20	0.31	> 1.3 ug/mL
S. Pneumoniae serotype 4 IgG	0.93	1.16	> 1.3 ug/mL
S. Pneumoniae serotype 5 IgG	0.50	0.74	> 1.3 ug/mL
S. Pneumoniae serotype 6A IgG	0.2	0.33	> 1.3 ug/mL
S. Pneumoniae serotype 6B IgG	0.51	0.80	> 1.3 ug/mL
S. Pneumoniae serotype 7F IgG	0.69	1.09	> 1.3 ug/mL
S. Pneumoniae serotype 9V IgG	0.44	**1.95 #**	> 1.3 ug/mL
S. Pneumoniae serotype 14 IgG	1.02	**3.71 #**	> 1.3 ug/mL
S. Pneumoniae serotype 18C IgG	0.96	1.06	> 1.3 ug/mL
S. Pneumoniae serotype 19A IgG	1.05	**2.49 #**	> 1.3 ug/mL
S. Pneumoniae serotype 19F IgG	1.2	0.98	> 1.3 ug/mL
S. Pneumoniae serotype 23F IgG	2.1	**3.42 #**	> 1.3 ug/mL
Protective serotypes after Pneumovax 23	8%	38%	>/= 70% of serotypes
Serotypes showing a 2-fold increase		30%	>/= 70% of serotypes

in coordinating immune cell activity in different arms of the immune system. Clinically, the IEI spectrum comprises five pillars that describe how IEI patients can present, which include infections, allergic disease, autoimmunity, lymphoproliferation and malignancy. The simplest way to understand the pathophysiology of the five pillars is to think of the immune system as a two-way mixer tap that adjusts the occurrence of infections in the host. Positive immune selection of broadly-reactive aggressive lymphocytes eliminates most infections with high efficiency, but also destroys surrounding normal tissue. Positive selection of lymphocytes with subdued reactiveness prevents tissue damage, but allows pathogens and tumours to take hold. A balance must be struck, and several immune checkpoints exist for this purpose in central (bone marrow, thymus) and peripheral (spleen, lymph nodes) tissues. These are sites where immature B- and T-cells undergo positive (central) and negative (peripheral) selection for reactivity to foreign and self-antigens. Poorly reactive and autoreactive lymphocytes are eliminated through apoptosis. Mutations that block the differentiation of Tfh or T-reg cells, or transcription factor mutations that enhance proliferation of lymphocytes, may enable immature or poor-quality lymphocytes to bypass these checkpoints, with downstream consequences such as immunodeficiency, autoimmunity and lymphoproliferation.[8]

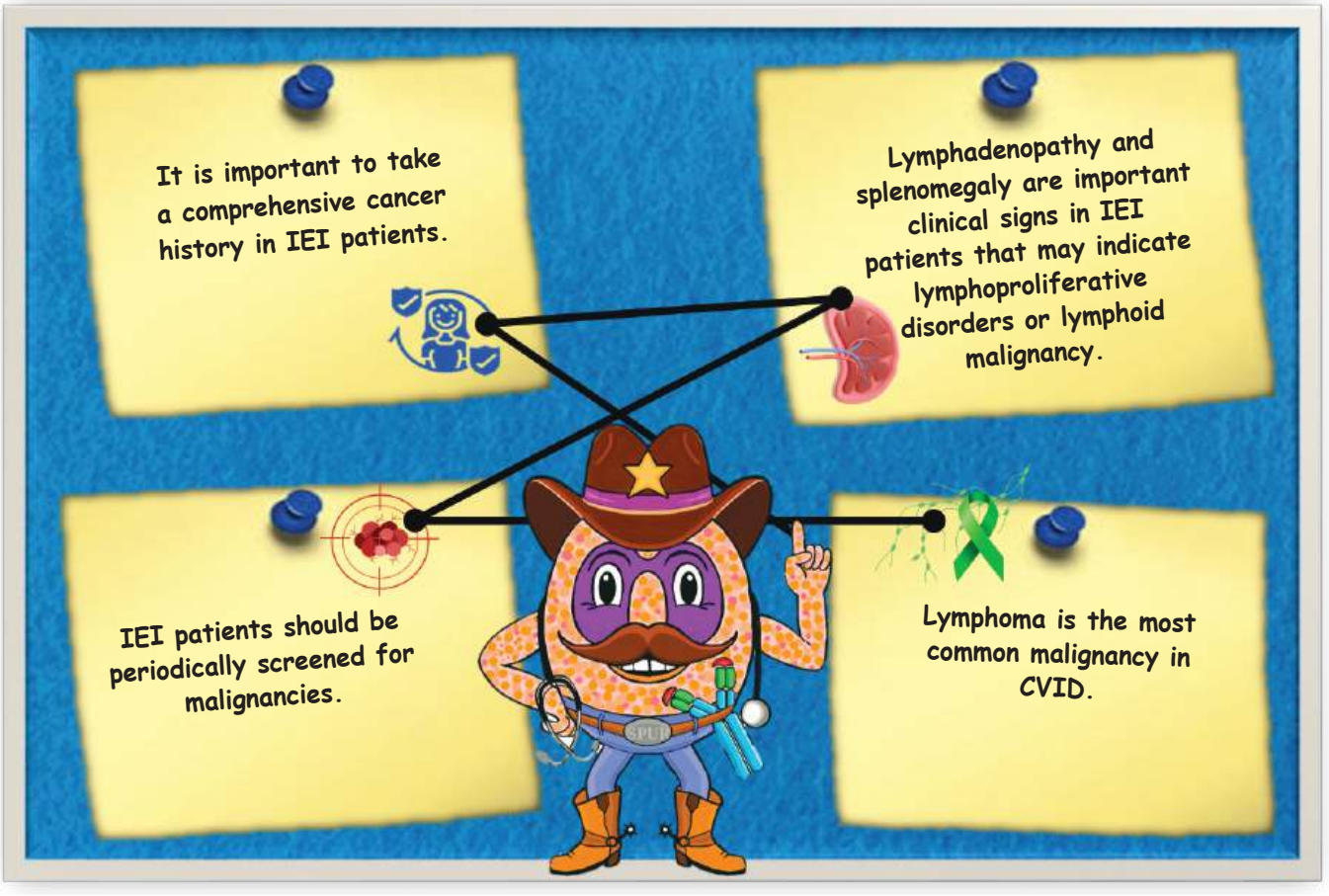
It is important to note clinical signs and systemic symptoms of lymphoproliferation and lymphoid malignancy when managing patients with IEIs. Suggestive systemic symptoms of cancer include fatigue, weight loss, night sweats and recurrent fever or easy bruising. Clinically, lymphoproliferation may present as lymphadenopathy, splenomegaly, hepatomegaly or any lymphocytic infiltration of an organ or tissue.[9] Splenomegaly is found in 26% of CVID patients, and frequently coexists with granulomatous disorders like IBD and granulomatous-lymphocytic interstitial lung disease (GLILD).[10] Lymphomas may develop in the spleen, lymph nodes, bone marrow, gastrointestinal tract, parotid gland, thyroid, lung and central nervous system. Positron emission tomography (PET) is useful to identify areas to biopsy.[10] On a lymph node biopsy, lymphoproliferation often appears as atypical or reactive hyperplasia, with granulomatous infiltration and absence of plasma cells.[10] Ebstein Barr virus (EBV) is a well-known oncogenic virus that infects and transforms B-cells, and is causally linked to lymphoproliferative disorders like lymphoma, Hodgkin's disease, non-Hodgkin lymphoma and

hemophagocytic lymphohistiocytosis (HLH) in IEI patients. It also causes other malignancies like nasopharyngeal carcinoma and gastric carcinoma.[15] In the general population, it causes mostly asymptomatic infections or infective mononucleosis (a self-limiting lymphoproliferative disease).[15] Persistence of EBV viral DNA in B-cells is lifelong, with periodic viral shedding in saliva. EBV infected B-cells are cleared by NK cells, CD4+ T helper cells and CD8+ cytotoxic T-cells. Genetic mutations in IEI patients may compromise immunological EBV control by undermining interactions between B-cells, T-cells and NK cells. Some IEI patients therefore have persistent EBV viraemia and lymphoproliferation, and ultimately develop EBV-associated lymphomas.[15] EBV-positive lymphoproliferation is therefore a very important risk factor for lymphoid malignancies in IEI patients, and an EBV viral load should be measured periodically to identify patients at increased risk. Rituximab is useful to suppress EBV replication in IEI patients with lymphoproliferation and persistent EBV viraemia.[16] Rituximab is an anti-CD20 monoclonal antibody that eliminates EBV-infected B-cells, and may reduce the risk of EBV-associated lymphoma. Lymphoma is a serious complication in IEI that reduces survival. As in the general population, lymphoma management relies on surgical resection, chemotherapy, radiation and Rituximab.[13,14,16,17]

IEI patients are at ten-fold higher risk of malignancy than the general population, and should also be screened periodically for non-haematological cancers. Other malignancies reported in CVID include leukaemia, gastric cancer, breast cancer, skin cancer, lung cancer, thymic cancer and melanoma.[12] Cancer screening in CVID involves the same age-appropriate cancer-screening programmes as for the general population.[13] In addition, they should be screened and treated for chronic infections that predispose to gastric cancer, like *H. pylori*, *cytomegalovirus (CMV)* and *human herpes virus 8 (HHV 8)*.

CVID patients are routinely managed with immunoglobulin replacement therapy (IRT) and antibiotic prophylaxis to control infections.[14] If there is a productive cough, sputum microscopy, culture and sensitivity is recommended to detect infections early.[14] Patients receiving IRT should be screened regularly for hepatitis B and C infection, and chronic liver disease.[14] Autoimmune diseases such as autoimmune thrombocytopenic purpura (ITP) and autoimmune haemolytic anaemia (AIHA), and granulomatous disorders of the lungs and gastrointestinal tract, may develop over time and should be appropriately managed with corticosteroids, immunosuppressants and biological agents (Rituximab, Infliximab and Etanercept) to preserve organ function.[14] CVID patients with enteropathy should be periodically screened by stool PCR for chronic infections caused by *Giardia lamblia* and norovirus.[14] Clinically stable patients well-established on IRT or antibiotic prophylaxis, and without target-organ complications, can be followed up annually. Patients with complications should be followed up 3–6 monthly. Implementation of preventative strategies and pro-active disease management have in recent years lowered the ten-year mortality rate in CVID from 20–40% to 5–10%.[14]

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

Dots connected. Please do screen for lymphoma and other cancers in IEI patients.

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