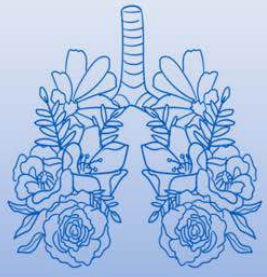
DR SPUR'S MYSTERY CASE

The Case of Asthma, Autoimmunity and an Unexpected Diagnosis

Welcome to Dr Spur's Immunology Clinic
Referral letter:



Dr Terry Cloete

Pulmonologist

814 Montreuil Avenue
Northriding
Sandton
9518

Tel: 086 123 9999

Dear Dr Spur,

Thank you for seeing this 27-year-old woman referred from my practice for recurrent lower respiratory tract infections, chronic sinusitis and worsening eczema. Her main complaints are fatigue, weight loss and joint stiffness over the past year. She was previously diagnosed with asthma (due to persistent wheeze since adolescence), autoimmune thyroiditis and a psoriasis/eczema overlap.

Her family history is notable for the death of a sibling in early childhood from pneumonia.

Given the frequency and nature of her infections, combined with signs of immune dysregulation, I was concerned about an inborn error of immunity and proceeded with further investigations.

Investigations

Full Blood Count (FBC):

- Mild lymphopaenia (total lymphocytes: 1.59 × 10^9/L), which is low-normal.

Immunoglobulins:

- IgG: 2.5 g/L
- IgA: < 0.06 g/L
- IgM: 2.9 g/L

→ Findings consistent with dysgammaglobulinaemia.

Vaccine Response Testing:

Pre-vaccine testing

- Tetanus IgG: 0.05 IU/mL
- *S pneumoniae* 23 serotypes: All below 1.3 ug/mL

Post-Adacel Quadra and Pneumovax 23 vaccination:

- Tetanus IgG: 0.09 IU/mL
  → Indicates insufficient T-cell-dependent vaccine responses.
- *S pneumoniae* serotypes: only one serotype showed a twofold rise in titre (normal response should be a twofold increase in > 70% of the tested serotypes)
  → Indicates insufficient T-cell-independent vaccine responses.

Lymphocyte Subsets:

- CD3+ T cells: low
- CD4+ and CD8+ T cells: low
- CD19+ B cells: present
- CD16/56+ NK cells: low

→ T^- B^+ NK^- phenotype.

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T-cell Proliferation (recall antigens to tetanus, varicella and candida):
- Reduced
  → Suggests T-cell dysfunction.

Autoantibodies:
- Positive ANA 1:1280. Speckled pattern with SSA antibodies and anti-TPO
  → Consistent with autoimmune involvement.

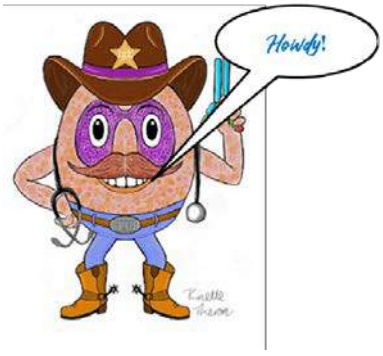
Chest CT:
- Bronchiectasis and ground-glass changes
  → Evidence of chronic lung injury due to infection.

Fraction of Exhaled Nitric Oxide (FeNO):
- 18 ppb
  → Within normal range; no evidence of aberrant pulmonary Type 2 inflammation.

Based on the above, I have made a working diagnosis of common variable immunodeficiency (CVID) with associated T-cell dysfunction. She has started immunoglobulin replacement therapy (IVIG) and antimicrobial prophylaxis (azithromycin 250 mg three times weekly). She is also under the care of a rheumatologist for autoimmune management. Despite this, she continues to experience significant fatigue and impaired daily functioning.

I would value your opinion on further management.

Warm regards,
Dr Terry Cloete
Pulmonologist



Dear Dr Cloete,

Thank you for the referral. This case raises concern for an underlying combined immunodeficiency, given the significant T-cell impairment and inadequate responses to both T-cell-dependent and T-cell-independent vaccines.

Further supporting this suspicion, she has also been diagnosed with a SIN 1 cervical lesion by her gynaecologist, attributed to chronic human papillomavirus (HPV) infection, and she experiences recurrent oral herpes simplex virus (HSV) lesions – both indicative of impaired antiviral defences.

As part of the workup, I proceeded with advanced genetic testing to evaluate for a monogenic cause of combined immunodeficiency, including conditions such as RAG1/2 or DOCK8 deficiency. The results confirmed a compound heterozygous mutation in the RAG1 gene, associated with partial V(D)J recombination activity, consistent with a diagnosis of leaky SCID due to a hypomorphic variant.

Leaky SCID refers to hypomorphic mutations in genes typically associated with severe combined immunodeficiency (SCID), which results in residual immune function and delayed presentation – often in adolescence or adulthood. A hypomorphic mutation is a genetic change that doesn't completely 'shut down' a gene but results in partial loss of gene function. It produces reduced (but not absent) activity, which leads to milder or delayed symptoms of a disease. These cases fall under the broader umbrella of combined immunodeficiency (CID), which is characterised by T-cell dysfunction either with or without B-cell/NK-cell involvement. Unlike classical SCID,

which presents in infancy, leaky SCID may go unrecognised for years due to milder or atypical symptoms.[1-3]

Presenting features

Adults with leaky SCID or CID may present with:

- recurrent sinopulmonary infections (eg, pneumonia, sinusitis, bronchiectasis);
- chronic viral infections (eg, HPV, HSV, molluscum contagiosum);
- autoimmune disease (eg, cytopaenias, thyroiditis, psoriasis, inflammatory bowel disease);
- allergic manifestations, eczema, or asthma-like symptoms;
- failure to thrive, fatigue or weight loss;
- a family history of early childhood deaths or recurrent infections.

Patients with combined immunodeficiency (CID) are frequently misdiagnosed with asthma because of overlapping respiratory symptoms such as chronic cough, wheezing and recurrent lower respiratory tract infections. These symptoms mimic the clinical features of asthma, especially when they occur early in life or in the absence of a clear immunodeficiency diagnosis.

However, in CID, the underlying issue is not airway hyperresponsiveness but immune dysfunction, leading to persistent or recurrent infections, which in turn cause airway inflammation and damage. Over time, this can result in bronchiectasis, further mimicking or complicating an asthma diagnosis. In addition, standard asthma treatments (such as inhaled corticosteroids or bronchodilators) may offer limited or no improvement, which should prompt re-evaluation.

A delay in recognising CID may occur because initial immune workups are often normal or not performed early, especially if infections appear to be 'responsive' to antibiotics.[4]

While leaky SCID is classically thought of as an immune deficiency, its clinical reality often includes profound immune dysregulation, with autoimmunity being a common and sometimes early feature. This apparent paradox – an immune system that is both underactive and self-reactive – can be understood by looking more closely at the nature of T- and B-cell development in leaky SCID.

In patients with hypomorphic mutations in genes such as RAG1/2 there is impaired V(D)J recombination, which limits the diversity of T-cell receptors. This defect hampers the thymic selection process, particularly negative selection, where autoreactive T cells should be eliminated. As a result, some of these self-reactive T cells escape into the periphery, where they can initiate or sustain autoimmune responses.

Compounding this issue is the dysfunctioning of peripheral tolerance mechanisms. Patients with leaky SCID often have reduced or abnormal regulatory T-cell (Treg) populations. These cells play a vital role in suppressing autoreactive lymphocytes and maintaining immune homeostasis. When Tregs are deficient or dysfunctional, autoreactivity can go unchecked, leading to autoimmune manifestations such as cytopaenias, thyroiditis, eczema or even lupus-like features.

B-cell involvement also contributes to this dysregulation. Although B cells may be present in leaky SCID, their function is often abnormal. In the absence of proper T-cell help and germinal centre regulation, B cells can become hyperactivated or misdirected, resulting in the production of autoreactive antibodies. Dysregulated class switching and impaired memory B-cell responses are often seen, adding to the autoimmune phenotype.

In addition, chronic or persistent infections, which are common in these patients due to their immunodeficiency, may act as persistent immune stimuli. This can lead to the bystander activation of lymphocytes and further disrupt the already fragile balance of immune regulation. Chronic viral infections, such as those with HPV or HSV, are particularly relevant triggers in this setting.

Therefore, in leaky SCID, the combination of impaired central tolerance, defective Treg-mediated suppression, abnormal B-cell function and chronic immune activation forms a 'perfect storm' for the development of autoimmunity. Recognising this overlap is key to understanding the full clinical spectrum of combined immunodeficiency disorders – and to managing them effectively.[5–7]

In combined immunodeficiency (CID), patients experience recurrent viral infections primarily due to impaired T-cell function, which plays a central role in controlling viruses. T cells, especially CD8+ cytotoxic T lymphocytes, are critical to identifying and eliminating virus-infected cells. When these cells are absent, reduced in number or functionally impaired – as is the case in CID – the immune system cannot clear viral infections effectively.

Moreover, CD4+ helper T cells are essential to coordinating the antiviral immune response, supporting both cytotoxic T cells and B cells in producing neutralising antibodies. In many forms of CID, both T- and B-cell responses are compromised, which results in poor viral clearance and chronic or recurrent infections with viruses such as HSV, HPV, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and molluscum contagiosum.

Even when B-cells are present, without proper T-cell help, antibody responses are often inadequate. This creates an environment in which viruses persist, reactivate or cause more severe disease than in immunocompetent individuals.[8]

Patients with combined immunodeficiency (CID) often develop allergic manifestations, including eczema, due to immune dysregulation rather than classic allergic pathways. Impaired T-cell function – especially a deficiency in Tregs – disrupts the balance between pro-inflammatory and anti-inflammatory signals. This imbalance can lead to Th2-skewed immune responses, which promote IgE production, eosinophilia and allergic inflammation. In addition, impaired skin-barrier function, chronic infections and microbial dysbiosis may trigger eczema-like rashes and allergic symptoms further. These presentations can resemble atopic dermatitis but often occur alongside signs of immunodeficiency such as infections

or autoimmunity, highlighting the underlying immune dysfunction.[7]

Diagnostic Work-Up

A high index of suspicion is required. Key investigations include:

1. Full blood count (FBC):
   - May demonstrate lymphopaenia, particularly affecting T-cells or other cytopaenias, due to autoimmune destruction.
2. Immunoglobulin Levels:
   - Hypogammaglobulinaemia or dysgammaglobulinaemia often present.
3. Vaccine response testing:
   - Poor response to protein (eg, tetanus) and polysaccharide antigens (eg, Pneumovax 23).
4. Lymphocyte subsets:
   - $T^-B^+NK^-$ or $T^-B^+NK^+$ phenotypes, depending on the gene involved.
5. T-cell function:
   - Poor proliferation to mitogens or recall antigens (eg, candida, tetanus, varicella).
6. Genetic testing:
   - Identification of hypomorphic mutations in genes such as RAG1/2, IL2RG, DOCK8, ZAP70, etc. An Inborn Error of Immunity Genetics panel can be requested.

Management

- Immunoglobulin replacement therapy (IVIG or SCIg) is essential to prevent infections.
- Prophylactic antimicrobials (eg, Trimethoprim-Sulfamethoxazole, azithromycin) for opportunistic (eg, *Pneumocystis jirovecii* pneumonia) and other respiratory infections.
- Autoimmune management often involves a multidisciplinary team (eg, rheumatology, dermatology).
- Hematopoietic stem-cell transplantation (HSCT) may be considered, especially in progressive cases or those with severe T-cell defects.
- Genetic counselling for patients and families.[4]

Conclusion

Adult-onset CID, including leaky SCID, is an under-recognised cause of recurrent infections and immune dysregulation. Diagnosis relies on clinical suspicion, functional and immunophenotyping studies and genetic testing. Early recognition can alter the disease trajectory significantly and improve quality of life.

Dr Spur's take-home message:

Dr Spur's mystery solved:

Dr Spur's mystery case solved: when asthma and autoimmune disease weren't the whole story: a case of adult-onset combined immunodeficiency

AUTHORS

Sylvia van den Berg,[1,2] Marieke Brauer,[1] André van Niekerk[2]

1 Department of Immunology, Ampath Laboratories, South Africa

2 Department of Paediatrics and Child Health, Steve Biko Academic Hospital, University of Pretoria, South Africa

ILLUSTRATORS:

Rinette Theron, Marlene Buitendach

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