

Chronic mucocutaneous candidiasis—more than just skin deep

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Case presentation

A 24-year-old Chinese man was referred to the Chest Unit of Grantham Hospital, Hong Kong in June 2016 for management of bronchiectasis. The patient had experienced his first episode of lower respiratory tract infection (LRTI) at age 17 years, which required hospital admission for intravenous antibiotics. He had since developed four to five episodes of LRTI annually and subsequently developed bronchiectasis with daily copious sputum and occasional haemoptysis.

Review of the patient's records revealed a history of autoimmune hypothyroidism since age 12 years, which was based on thyroid scintigraphy and high titres of antithyroid autoantibodies and required thyroxine replacement. At age 21 years, after an incidental finding of iron deficiency anaemia, the patient underwent upper endoscopy, which revealed oesophageal candidiasis (Fig 1). The patient

had recurrent and chronic oral ulcers, and excisional biopsy with Grocott staining displayed fungal spores and pseudohyphae consistent with candidiasis.

Further questioning of the patient revealed frequent tinea infections and orogenital candidiasis since early childhood. The patient had had childhood chickenpox with two further episodes of zoster reactivation during his teens. There were no features suggestive of atopy nor any history of recurrent abscesses. The patient had difficulty attending his frequent medical appointments and often required sick leave from his work as a technician. He was a never smoker and social drinker. The patient was born and raised in Hong Kong, and had received all routine vaccinations without problems. The family history was unremarkable with no history of consanguinity. The patient lived with his parents and younger brother, none of whom had candidiasis.

High-resolution computed tomography revealed bilateral lower lobe bronchiectasis (Fig 2) and bronchoscopy again showed extensive candidiasis with no airway abnormalities. Pulmonary function test results and serum alpha-1-antitrypsin level were normal. Sputum cultures were negative for acid-fast bacilli and yeasts, and aerobic culture yielded

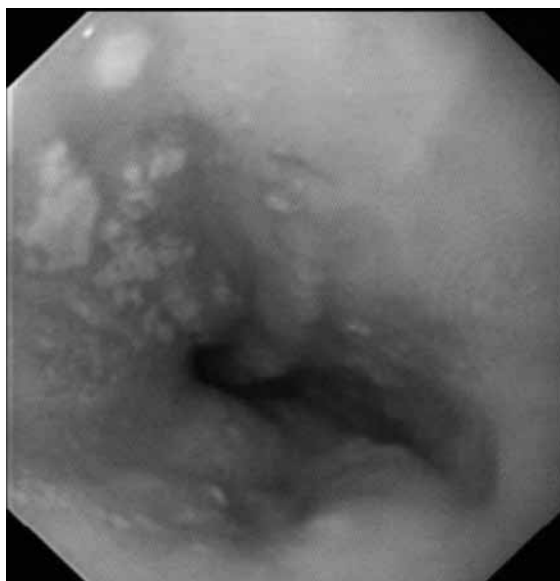


FIG 1. Oesophageal candidiasis on upper endoscopy



FIG 2. Bronchiectasis on high-resolution computed tomography

commensals only. The patient's complete blood counts were grossly normal apart from a persistently low absolute lymphocyte count ($0.5\text{--}0.7 \times 10^9/\text{L}$). Immunoglobulin (Ig) levels (IgG/IgM/IgA/IgE) were all within normal limits. Screening for diabetes mellitus and testing for human immunodeficiency virus (HIV) was negative. Complement levels and the dihydrorhodamine assay were normal. A serology panel also found positive anti-nuclear antibodies with a titre of 1:320, in addition to previously documented thyroid autoantibodies. Repeated lymphocyte subsets showed persistent panlymphocytopenia (CD19:43/ μL [n:91-452], CD3:491/ μL [n:938-2311], CD4:206/ μL [n:437-1226], CD8:263/ μL [n:322-1104] and CD16/56:115/ μL [n:177-1059]), with impaired lymphocyte proliferation after phytohaemagglutinin and pokeweed mitogen stimulation.

In view of his chronic mucocutaneous candidiasis (CMC), autoimmunity and combined immunodeficiency, the patient was referred to us for further evaluation. An interleukin (IL)-17-related defect was suspected and sequencing of the signal transducer and activator of transcription (STAT) 1 gene was performed. A previously reported gain-of-function (GOF) mutation of p.G384D in the DNA-binding domain was identified.¹ The patient was counselled and long-term itraconazole and co-trimoxazole prophylaxis treatment was started. Measurement of pneumococcal antibody responses were scheduled. The patient continues to receive multidisciplinary care between immunology, pulmonology, and internal medicine after a unifying diagnosis for his wide spectrum of disease manifestations was made.

Discussion

That primary immunodeficiencies (PIDs) only affect children is a common misconception. Diagnoses are also made in adulthood due to genuine adult-onset types, as in our case, or delayed disease recognition. We describe the first reported adult case of STAT1-GOF mutation in our locality. The patient had a typical history of CMC, complicated by recurrent infections, bronchiectasis, and autoimmune hypothyroidism. The patient also had panlymphocytopenia, which is reported in 20% to 30% of STAT1-GOF patients and associated with LRTIs.² The first possible indication of STAT1-GOF mutation was the autoimmune hypothyroidism in the context of CMC.

Typically, CMC is characterised by persistent/recurrent non-invasive *Candida* infections of the skin, nails, and mucous membranes. Candidiasis is usually an opportunistic infection and associated with immunosuppression acquired through diabetes mellitus or HIV, or use of chemotherapy, glucocorticoids, or antibiotics. Candidiasis is also associated with a variety of PIDs, usually with

an underlying IL-17 pathway defect. Examples include hyper-IgE syndromes, autoimmune polyendocrinopathy syndrome type 1, CARD9 deficiency, in addition to IL-17F and IL-17RA deficiencies.³

Since 2011, STAT1-GOF mutations have been discovered that cause autosomal dominant familial CMC. These mutations are now established as the most common genetic cause of inherited CMC. Such STAT1-GOF mutations have also been reported in paediatric patients in Hong Kong with CMC and penicilliosis.⁴ These mutations impair STAT1 dephosphorylation and enhance the production of STAT1-dependent cytokines (interferon- α/β , interferon- γ and IL-27). In turn, this likely represses STAT3-dependent gene transcription and impairs the development of IL-17-producing T cells, although the exact mechanisms remain unclear.⁵

A recent analysis of the clinical manifestations in 274 individuals with 76 different STAT1-GOF mutations revealed an extremely broad disease phenotype.² In addition to CMC, patients were also prone to other fungal, bacterial (usually LRTIs), and viral infections. Results of immunological investigations were variable, but abnormalities were significantly associated with increased infections. More than a third of patients had autoimmune/inflammatory disorders, most commonly hypothyroidism, and 21% of patients had bronchiectasis.² Most patients with autoimmunity had positive autoantibodies. Alarmingly, these patients are more likely to develop other autoimmune disorders, cerebral/abdominal aneurysms, and squamous cell carcinomas (likely secondary to chronic mucocutaneous inflammation).

The outcome for patients with STAT1-GOF mutations remains poor, with most deaths resulting from infection, aneurysms, or malignancies. Long-term (as opposed to intermittent) systemic antifungal therapy remains the mainstay of treatment, aiming to reduce the development of antifungal resistance and malignancy. Additional antibiotic prophylaxis and intravenous Ig should be considered for patients with recurrent infections. In our patient, intravenous Ig would have been indicated if his response to pneumococcal vaccination was suboptimal in the context of bronchiectasis. Furthermore, autoimmune hypothyroidism is associated with cerebral aneurysms and baseline magnetic resonance angiography may be indicated. Lastly, any ear, nose, and throat or gastrointestinal symptoms should alert the physician to a need for regular monitoring of such malignancies with biopsy. Experimental therapies such as colony-stimulating factors and ruxolitinib, a Janus kinase 1/2 inhibitor, have been reported to successfully improve CMC and will merit a trial if his CMC worsens with time.⁶

For other PIDs, the main goals are to reduce the

incidence of infections and to prevent development of complications; with the ultimate aim of cure. Improved awareness and further development of adult clinical immunology in Hong Kong is required, so that adult patients with PID receive more timely and comprehensive care.

Author contributions

All authors have made substantial contributions to the concept; acquisition of data; interpretation of data; drafting of the article; and critical revision for important intellectual content.

Declaration

All authors have disclosed no conflicts of interest. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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