Patient Oriented Problem Solving (POPS) Case Report

Fifty-five-year-old man with chronic yeast infections

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ABSTRACT

As immunologists, we are frequently asked to evaluate patients with recurrent infections. These infections can provide us with clues regarding what pathways might be aberrant in a given patient, e.g., specific pyogenic bacteria with Toll-like receptor problems, atypical mycobacteria with interferon gamma receptor autoantibodies, and Candida/staphylococcal infections with cellular immune abnormalities. We present a 55-year-old man who presented to our immunology clinic with onychodystrophy of the toenails and fingernails and recurrent oral–esophageal candidiasis. The differential diagnosis for recurrent yeast infections is complex and includes usual suspects as well as some that are not as straightforward.

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CASE PRESENTATION

Chief Complaint

Onychomycosis and recurrent oral–esophageal candidiasis.

History of Present Illness

A 55-year-old man was referred to the University of Virginia Immunology Clinic for onychodystrophy of his fingernails and toenails and recurrent oral–esophageal candidiasis. He had the problem with his toenails since childhood, but this had subsequently spread to involve his fingernails ~4–5 years ago. Six months previously, he was diagnosed with oral candidiasis and was successfully treated with nystatin. He had no history of antibiotic or corticosteroid usage. One week later, he again developed thrush, and this pattern continued over the next months. Concomitantly, he was evaluated by the Dermatology Department for the onychodystrophy. Fingernail cultures were positive for Candida and his toenails grew dematiaceous mold. He was treated with fluconazole or itraconazole at various times over the past year and noted improvement with these treatments. Again, once the medications were removed, his symptoms returned. His last course of antifungal medication was completed 2 weeks before presenting to our clinic.

During our evaluation, he reported early dysphagia, especially while eating bread. He also described symptoms of gastroesophageal reflux and cough that were persistent and exacerbated after both eating and exercising. The cough would resolve with his ongoing antifeast treatments. He denied constitutional symptoms as well as sinopulmonary, gastrointestinal, blood, bone, central nervous system, or kidney infections. He denied recurrent herpes, varicella, or human papilloma virus infections. Most importantly, he denied infections with Staphylococcus aureus including furunculosis. He had no history of autoimmune disease such as thyroiditis, autoimmune hemolytic anemia, or idiopathic thrombocytopenic purpura, although he did report transverse myelitis that developed temporally to receiving the tetanus and influenza vaccinations, ~17 years before presenting to our clinic. He had no human immunodeficiency virus (HIV) risk factors.

Physical Examination

On physical examination his oropharynx was without evidence of oral candidiasis. He had no lymphadenopathy and his respiratory exam was normal. Skin examination did not show atopic dermatitis or furunculosis; however, he had significant onychodystrophy of his fingernails and toenails.

Laboratory and Other Diagnostic Findings

Our initial immunologic evaluation showed absent delayed-type hypersensitivity testing to Candida and
**Trichophyton**, at 48 hours. He was diagnosed with chronic mucocutaneous candidiasis (CMC). His complete blood count revealed normal numbers of neutrophils, lymphocytes, and monocytes, but, interestingly, he had no eosinophils or basophils (Table 1). Flow cytometry (Table 1) showed a low CD4:CD8 ratio with low–normal absolute CD4 T-cell numbers (585/9262 L) but was very surprising for the complete absence of CD19 B cells. The absence of B cells was subsequently confirmed with enumeration of CD20 cells, which were also absent. Because of the absence of B cells, quantitative immunoglobulins were measured and, along with specific antibody testing, these were surprisingly unremarkable (Table 1).

**Clinical Course**

A chest computed tomography scan showed the presence of a large anterior mediastinal mass. He was referred to thoracic surgery for video-assisted thoracoscopy with thymectomy. Pathology showed a non-invasive type B1 thymoma with a lymphocytic predominance but no spindle cells. A repeat computed tomography chest scan at 6 months follow-up did not reveal recurrence of his anterior mass. Interestingly, IgG levels have remained normal postthymectomy and IgG level at 6-month follow-up was 921 mg/dL.

**QUESTION 1**

**What Is the Differential Diagnosis of CMC?**

CMC is the result of the failure of T lymphocytes to mount a cellular immune response to *Candida*, leading to chronic Candida infections that are typically limited to mucosal surfaces, skin, and nails. CMC can present as a manifestation of a wide number of underlying conditions. Most commonly, CMC is a component of the myriad of infections associated with the comprehensive loss of T-cell function that occurs, *e.g.*, in severe combined immune deficiency, DiGeorge syndrome, HIV, *etc.* Any patient with CMC should be HIV tested. In addition to negative viral load, our patient had normal numbers of CD4 T cells (Table 1), which, along with his age, eliminated severe combined immune deficiency or other acquired or idiopathic CD4 lymphopenias as a mechanism for his disease.

The immune response to *Candida* requires complex interactions between immune cells and the yeast for
adequate recognition, engagement of innate and adaptive immune responses, phagocytosis, and killing. Innate immunity includes a combination of monocytes, macrophages, neutrophils, dendritic cells, and others that together maintain homeostasis with this usual commensal organism, using Toll-like receptors (TLR2 and 4), complement receptors (CR3), and numerous pattern recognition receptors, such as the C-type lectin receptors (CLR; macrophage mannose receptor, Dectin-1, DC-sign, etc.) that are necessary for recognition of mannans and mannoproteins within the cell walls of Candida albicans.1 For the development of adaptive, largely Th17-mediated immunity, binding of Dectin-1 on the surface of dendritic cells signals the CARD9 complex, ultimately activating the production of cytokines including transforming growth factor (TGF) β, IL-6, and IL-23.2 These cytokines provide “signal 3” for the adjacent T cells, which are simultaneously having Candida antigen presented by the dendritic cells. In the context of cellular differentiation, signal 1 refers to major histocompatibility complex/T-helper cell interactions, and signal 2 refers to costimulatory molecules CD80/86 integrating with their respective ligands. Signal 3 represents the cytokine milieu that supports T-cell activation and promotes T-helper immune deviation. In the generation of Th17 cells, the cytokine milieu required includes TGF-β, IL-6, and IL-23. These cytokines signal through tyrosine kinase 2 (Tyk2) to activate the nuclear transcription factor STAT3. These signaling molecules and, especially, STAT3, lead to the production of IL-17 and the differentiation of Th17 cells.3,4 Mutations in genes encoding these proteins and others can lead to Th17 deficiencies and the diagnosis of CMC (Table 2; Fig. 1).

STAT3-deficient (hyper-IgE syndrome) patients are defined by their markedly elevated IgE levels and, in further contrast to this patient, are generally hypereosinophilic and show susceptibility to skin and respiratory Staphylococcus infections (along with the candidiasis).5 Mutations in dedicator of cytokinesis 8 (Dock8) and Tyk2 are also characterized by elevated serum IgE levels, eosinophilia, sinopulmonary staph infections, and lymphopenia along with the CMC. These are autosomal recessive (AR) conditions that are largely distinguished from autosomal dominant hyper-IgE syndrome by the presence of frequent cutaneous viral infections and defects in humoral immunity (e.g., low IgM).6–10

IL-17F deficiency is an autosomal dominant condition in which the host displays impaired (but not abolished) activity against Candida, possibly reflecting the continuing presence of IL-17A. In contrast, IL-17RA deficiency is an AR condition that completely abolishes cellular responses to both IL-17A and IL-17F11 and thereby produces a much more severe defect in anti-Candida immunity. Complete STAT1 deficiency leads to diminished STAT1-dependent cellular responses to both interferon (IFN) α/β as well as IFN-γ. Patients with this disease suffer from both severe viral infections (herpesviruses), as well as intracellular pathogens (Salmonella, BCG, and nontuberculous mycobacteria).12 Interestingly, gain of function autosomal dominant STAT1 mutations can develop infections similar to those with loss of function mutations but can also develop infections with dimorphic molds (Sampaio et al.13) as well as CMC and autoimmunity (Uzel et al.14). Although these patients have increased expression of cytokines that promote Th17 immune deviation (IL-6 and IL-21), ultimately, the stronger cellular responses to fungal elements, including, ultimately, the development of Th17 cells as discussed previously.17 Consistent with its essential role as a “danger signal” capable of recognizing Candida-derived fungal elements AR mutations in Dectin-1 and CARD9 have also been associated with the CMC phenotype. However, CARD9 defects are associated less with CMC but instead with severe invasive Candida infections, including meningitis18 (Table 2; Fig. 1).

Finally, autoimmune polyendocrinopathy ectodermal dystrophy results from AR mutations of the autoimmune regulator gene, which in contrast to our patient, is typically characterized by autoimmune hypoparathyroidism and adrenal insufficiency, along with CMC.19 CMC in this population has been linked to presence of autoantibodies against IL-17A, IL-17F, and IL-22,20,21 although diminished intrinsic Th17 responses have also been established.20

**QUESTION 2**

**How Does the Finding of Absent B Cells Affect This Differential?**

Absence of B lymphocytes can be seen in numerous conditions and in association with use of rituximab (anti-CD20 antibodies; Table 3). After we discovered our patient had no B cells, we broadened our differential diagnosis to include adult onset X-linked agammaglobulinemia caused by forme fruste mutations in the BTK gene. However, these B-cell deficiencies are not typically associated with CMC, and he lacked any of the typical presenting features suggestive of a humoral immune deficiency. As such, the most likely etiology of his acquired B-cell deficiency is Good's
| Differential Diagnosis of CMC | Clinical Characteristics | Genetic Mutations | Laboratory Abnormalities |
|-------------------------------|--------------------------|-------------------|--------------------------|
| Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy | Recurrent *Candida* infections, hypoparathyroidism, Addison’s disease; variable autoimmune endocrine associations | (Autoimmune regulator gene) | Autoantibodies against adrenal cortex, pancreatic β cells, and/or thyroid; Hypoparathyroidism; Hypocalcemia, hyperphosphatemia; Abundant autoantibodies including anti-IL-17A, IL-17F, IL-22, or others important for Th17 development or function |
| Hyper-IgE syndrome | Dermatitis, facial abnormalities, failure of primary dental deciduousness, pneumonia, and lung cysts | Loss of function in STAT3 gene | Elevated serum IgE of >2,000 IU/mL; Hypereosinophilia; Diminished Th17 cells |
| STAT1 | Recurrent *Candida* infections | Gain of function in STAT1 gene | Low proportions of circulating IL-17A and IL-22–producing T cells |
| Gain of function mutations | Aneurysms | | Cytokine responses such as IFN-α/β, IFN-γ, and IL-17 prevail to inhibit Th17 differentiation |
| STAT1 deficiency | Recurrent *Candida* infections; mycobacterial infections | Loss of function in STAT1 gene | Diminished Th17 cells |
| IL-17 F Mutations | Recurrent *Candida* infections | Autosomal dominant | Diminished function of Th17 cells; may be partial, because this disease only affects IL-17F leaving IL-17A functioning properly |
| IL-17 receptor mutations | Recurrent *Candida* infections | AR | Complete loss of responsiveness to both IL-17A and IL-17F |
| STK4 deficiency | Recurrent bacterial infections, viral infections, mucocutaneous candidiasis, cutaneous warts, and skin abscesses, and atrial septal defects | Homozygous premature termination mutation in the gene STK4 | T- and B-cell lymphopenia and intermittent neutropenia |
| Dectin-1 deficiency | Recurrent *Candida* and *Pneumocystis jirovecii* infections | Early stop-codon mutation Tyr238X | Absent *Candida*-specific Th17 cells |
| CARD9 | Recurrent fungal, viral and bacterial infections, particularly invasive *Candida* infections including meningitis | | Diminished Th17 cells |
syndrome. Good’s syndrome is a rare, adult-onset primary immunodeficiency, characterized by low or absent B cells, hypogammaglobulinemia, and multiple autoimmune diseases in the setting of an underlying thymoma. As with our patient, Good’s syndrome patients usually exhibit relative CD4 T-cell lymphopenia (low–normal in our patient), absent eosinophils and basophils, and present in the 4–5th decade of life.22,23 Additionally, our patient presented with symptoms concerning for a mediastinal process (difficulty swallowing). However, Good’s syndrome requires deficient IgG antibodies, and, at the time of evaluation, our patient’s immunoglobulins were normal, which is inconsistent with this diagnosis (see discussion later in text).

QUESTION 3
What Additional Investigations Would Be Helpful in This Patient to Determine How His Thymoma Produced CMC?

After informed consent, blood samples were taken from the patient. Flow cytometry was performed in the research laboratory at the National Institutes of Health to measure CD4+ T-cell lymphopenia, low or absent B cells, ± eosinopenia abundant variable autoantibodies including anti-IFN-α, IFN-ω, IL-12, IL-17, IL-22, and others important for Th17 development or function.
Table 3  Differential diagnosis for absent B cells

| Category          | Condition                                                                                       | Notes                                                                 |
|-------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Humoral immunodeficiency | Good’s syndrome                                                                                      | Adult-onset primary immunodeficiency, frequent opportunistic infections, and thymoma |
|                   | X-linked agammaglobulinemia (Bruton’s agammaglobulinemia): mutation in the gene coding for Bruton tyrosine kinase (BTK) | Female carriers have no clinical manifestations; accounts for 85% of agammaglobulinemia; recurrent otitis, sinusitis, and pneumonia; enterovirus |
|                   | μ (IgM) heavy chain deletion/mutation                                                              | Most common cause of AR agammaglobulinemia; recurrent otitis, sinusitis, and pneumonia; arrest occurs at the pro–B-cell level |
|                   | B-cell linker protein (BLNK)- defect in adaptor protein necessary for receptor signaling Igα and Igβ | Opportunistic infections, pre-B acute lymphoblastic leukemia |
|                   | Surrogate light chain and A5 deletion/mutation                                                      | Mutations result in arrest of maturation at the pro B-cell level |
| Malignancy        | Nijmegen breakage syndrome (NBS): AR disorder and NBS1 gene mutation                               | Recurrent otitis, sinusitis, and pneumonia (similar to μ heavy chain mutations) |
| Medications       | Rituximab- anti-CD20 monoclonal                                                                  | Recurrent infections, thymoma, and superior vena cava syndrome |

AR = autosomal recessive.

Figure 2. Evidence of Th17 deficiency by flow cytometry and autoantibodies. (A) IL-17a production (%) in CD4+ memory T cells (red circles) for normal (top panels) and patient peripheral blood mononuclear cells pre- and postthymectomy (middle and lower panels, respectively). Unstimulated (left panels) or stimulated with phorbol 12-myristate 13-acetate/ionomycin (right panels) conditions. (Right side of each panel shows interferon [IFN] γ-producing CD4+ memory T cells.) Unstimulated condition not available for prethymectomy sample because of lymphopenia. B) Anticytokine autoantibodies before and after thymectomy. Plasma was mixed with the cognate beads, washed, and tested against human IgG.
reflecting the role of the thymus in negative selection of autoreactive cells, we hypothesized that our patient would have autoantibodies to IL-17. We worked with our partners at the National Institutes of Health to evaluate for anticytokine autoantibodies. These studies showed autoantibodies to IFN-α, IFN-ω, IFN-λ3, and IL-12p70 but not to IL-17 (including A and F) or IL-22 (Fig. 2B). Further testing revealed no evidence of autoantibodies to granulocyte–colony-stimulating factor, granulocyte macrophage–colony-stimulating factor, IFN-β, IFN-γ, TNF-β, IFN-γ-inducible protein (CXCL10; IP-10), IL-4, IL-6, or IL-15.

Autoantibodies to IL-17 are thought to be one cause of CMC associated with thymoma, reflecting the subsequent loss of the ability of Th17 cells to carry out their antifungal (and antibacterial) immune functions. However, the absence of Th17 cells in our patient could be a reflection of defective T-cell development secondary to thymic dysfunction or could also be ascribed to autoantibodies to cytokines essential for Th17 immune development. Although IL-6 and TGF-β are the most important cytokines necessary for the generation of Th17 cells, other cytokines including IL-23 contribute. IL-23 is a heterodimer consisting of a unique IL-23α chain and the p40 chain of IL-12. Thus, autoantibodies to anti–IL-12p40 are capable of also targeting IL-23. We hypothesize that this could explain our patient’s depressed Th17 immunity (Fig. 3). Although we recognize that anti–IL-12p40 autoantibodies are prevalent in thymoma, without necessarily resulting in CMC, it is also likely that anticytokine autoantibodies can manifest differently, possibly depending on host and environmental factors, as well as differences intrinsic to the autoantibodies themselves.

**Table 4** Anti-cytokine antibodies and their associated diseases

| Autoantibody to Cytokine | Associated Disease(s) |
|--------------------------|-----------------------|
| IFN-α                    | Thymoma, myasthenia gravis, SLE, and viral infections |
| IFN-ω                    | Thymoma and myasthenia gravis |
| IL-12                    | Thymoma, myasthenia gravis, CMC, and other opportunistic infections |
| IL-22                    | CMC in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and thymoma |
| IL-17F                   | CMC in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and thymoma |
| GM-CSF                   | Pulmonary alveolar proteinosis, and cryptococcal meningitis |
| G-CSF                    | Felty’s syndrome (neutropenia) |
| Erythropoietin           | Pure red cell aplasia |
| IFN-γ                    | Opportunistic infections, especially nontuberculous mycobacterial infections |
| Osteoprotegerin          | Osteoporosis in celiac disease |

IFN = interferon; CMC = chronic mucocutaneous candidiasis; G-CSF = granulocyte–colony-stimulating factor; GM-CSF = granulocyte macrophage–colony-stimulating factor; SLE = systemic lupus erythematosus.

**Figure 3.** The role of autoantibodies to IL-12 in the development of chronic mucocutaneous candidiasis (CMC). The shared subunit p40 allows for antibody blockade of both Th1 responses via IL-12 and Th17 responses via IL-23. See text for details.

**DISCUSSION**

We speculated that as with other autoimmune syndromes associated with thymoma (e.g., myasthenia gravis), thymectomy might be associated with loss of his autoantibodies and restoration of his Th17 compartment. Because it is unknown if or even whether this could occur, we decided to start the patient on continuous fluconazole as prophylaxis. However, 1 year after thymectomy, we repeated anticytokine autoantibody testing, and it appears that the autoantibodies persisted against IFN-α, IFN-ω, IFN-λ3, and IL-12p70 (Fig. 2B). At this time, he remains on antifungal prophylaxis to manage his infections.
Surprisingly, despite his absence of B cells, our patient had normal immunoglobulins, reflecting the ongoing presence of long-lived plasma cells. The life expectancy of human plasma cells is presently not known. However, we can expect that at some time in the future he will become the “typical” Good’s syndrome patient and develop humoral immune failure. Furthermore, on biopsy, our patient did not have the typical histological finding in the thymus of spindle cells that are associated with Good’s syndrome. However, spindle cells are not required for the diagnosis of Good’s syndrome, and other cell types within the thymoma have been described, including epithelial cell tumors and/or mixed epithelial/lymphoid tumors.22

The absence of B cells in this disease is thought to also reflect an autoimmune process but, once the B-cell compartment is destroyed, this can never be restored even if these autoantibodies also resolve, presumably reflecting the absence of B lymphocyte stem cells. Although the timing of his humoral immune failure remains unclear, our patient will be monitored closely for infections and will have yearly quantitative antibody titers because we expect him to ultimately need to start replacement immunoglobulin therapy.

Final Diagnosis

This patient has a thymoma associated with autoantibodies to IFN-α and IL-12p70 and CMC. It is possible that his illness may progress in the future to be Good’s syndrome.

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