Understanding Chronic Mucocutaneous Candidiasis

This collection of disorders that cause cutaneous and fungal infections has just recently become better understood, but diagnosis still remains a challenge.

By Bob Geng, MD

PATIENTS WITH significant defects in cellular immunity have long been recognized to be susceptible to a variety of mucosal and systemic fungal infections. These include patients with primary combined immune deficiencies and cellular immunodeficiency syndromes who may present with both cutaneous and systemic fungal infections, one of which is chronic mucocutaneous candidiasis (CMCC).

The clinical phenomenon of CMCC has been recognized for decades, but the underlying mechanisms that lead to the disease have not been well understood until recently. Clinically, patients with CMCC present with chronic Candida infections of the nails, skin and mucous membranes. The most common species of Candida found in CMCC is Candida albicans. Some of the most recognized cases of CMCC have defined genetic causes,

some of which are associated with deficiencies in the innate immune system and defects of the TH17 pathway of adaptive cellular mucosal immunity. In addition to susceptibility to Candida infections, CMCC patients also often present with autoimmune endocrine and hematologic complications.

The most well-defined genetic defect associated with CMCC is the autoimmune regulator deficiency.

Specific Known Genetic Defects

In general, antifungal immunity is achieved through pattern recognition receptors of the innate immune system and T helper cells that help to defend the mucosal membranes and skin. Unlike receptors on T cells or immunoglobulin, the innate pattern recognition receptors are not specific to individual types or species of fungi to which the body is exposed; instead, they recognize general conserved features of all fungi organisms. The group of T helper cells involved in antifungal immunity and defense of the mucosal membranes and skin are the TH17 cells, which derive their name from their involvement in the production of a cell signaling molecule called IL-17. Defects that alter the normal number or function of TH17 cells or alter the expression of IL-17 will lead to impaired immunity against fungi, as well as decreased ability for the body to defend the mucous membranes and skin.

The most well-defined genetic defect associated with CMCC is the autoimmune regulator (AIRE) deficiency. AIRE accounts for most of CMCC cases in certain populations (Sardinians and Finns), but only a minority of cases of CMCC in the general population. Around 50 different mutations have been discovered thus far on this gene leading to CMCC. This specific defect leads to CMCC because AIRE, under normal conditions, prevents the proliferation of autoimmune T cells. During the process of T-cell development and maturation, those with receptors that recognize self are not allowed to expand to prevent the development of autoimmune disease. Normal functioning of AIRE is what allows this selection against autoimmunity to occur. Therefore, when AIRE is abnormal, these autoimmune T cells are allowed to expand and travel to the rest of the body. One of the manifestations of this autoimmunity is the impairment of the TH17 system. There is evidence that some of these autoimmune T cells induce B cells to produce antibodies that block the normal function of IL-17 and IL-22 (another cell-signaling molecule that is involved in the TH17 system). This impairment leads to a functional deficiency of the TH17 system's ability to defend against Candida infections.

In addition to the impact against the TH17 system due to AIRE deficiency, other forms of autoimmunity can occur such as in the endocrine system. The endocrine system is responsible for the production of various hormones essential for a body's healthy functioning. This is why patients with CMCC from the AIRE mutation can often develop hypoparathyroidism and adrenal failure. Patients with hypoparathyroidism can develop severely low calcium levels and low magnesium levels in the blood, and occasionally other endocrine disorders such as hypothyroidism, type 1 diabetes, growth hormone deficiency and decreases in the sex hormones. Collectively, both CMCC and endocrine abnormalities are called the autoimmune polyendocrinopathy candidiasis ectodermal dystrophy or the autoimmune polyendocrine syndrome type 1. It is often challenging to make this diagnosis since different features of the condition may occur in different individuals at different times in their lives. The first signs and symptoms may occur during infancy, but they can develop as late as young adulthood. Therefore, in patients with features of CMCC and endocrine defects, it is important to have a low threshold to suspect AIRE mutation.

Other known defects of the TH17 system associated with CMCC include gain-of-function mutations of the signal transducer and activator of transcription 1 (STAT1), as well as mutations directly on the IL-17 receptor. STAT1 actually leads to a functional decrease of IL-17 and IL-22 leading to a relatively impaired TH17 response, thus decreasing the defense against Candida. Unlike the AIRE mutations, these defects do not appear to directly result in autoimmune diseases of the endocrine system.

One well-described defect in the innate immune system leading to CMCC is dectin-1 deficiency. Components of Candida are recognized by various pattern-recognition receptors (toll-like-receptors 2 and 4 and mannose binding receptors). Dectin-1 works with these receptors to enhance production of cell-signaling molecules to defend against Candida infections. Therefore, deficiencies in Dectin-1 will lead to an impairment

of anti-Candida immunity. Again, similar to most forms of CMCC, patients with Dectin-1 do not develop systemic invasive Candida infections, and are susceptible only to Candida infections in the skin and mucous membranes. Another more recently described defect in the innate immune system is a specific mutation of the toll-like-receptor 3 (TLR3) that leads to features of CMCC. In addition, since TLR3 is very important in antiviral immunity, these patients also develop severe viral infections and chronic lung disease, some degree of autoimmunity involving the endocrine system and low blood cell counts.

Since antifungal immunity is a complex process, many other conditions will lead to susceptibility of both mucosal/cutaneous candidiasis and more serious invasive disease. Secondary immunodeficiencies such as HIV, poorly controlled diabetes or medication-induced immunodeficiency due to prolonged use of steroids can all increase the risk of developing fungal infections. Other primary immunodeficiency syndromes such as severe combined immunodeficiency, hyper-IgE syndrome and other forms of combined cellular and humoral immunodeficiency can also all lead to some degree of fungal infection. However, all these conditions have other clinical signs and symptoms that make them distinct from CMCC. Furthermore, it is important to distinguish these other conditions from CMCC since they have specific treatments, as well as potential susceptibility to more invasive systemic fungal infections.

Laboratory Evaluation

Diagnosis of CMCC is largely clinical, based on signs and symptoms of presentation. The only definitive laboratory diagnosis is based on genetic testing to detect specific known genetic defects associated with CMCC. However, there are some features of CMCC that may be found in standard immunologic testing. One of the more common laboratory findings in CMCC is the abnormality in both T-cell count and response to Candida antigen. In the usual cellular immune panel ordered for immunodeficiency evaluation, the T-cell numbers and T-cell proliferation may be reduced following Candida stimulation. Some patients may also demonstrate humoral immunity with decreased level of circulating immunoglobulin. This hypogammaglobulinemia could be manifested in a lower level of total IgG or in IgG subclasses, as well as functional defect seen as decreased response following vaccination with polysaccharide antigens (a selective antibody deficiency type of presentation). Testing for specific IgG to Candida is not helpful in the diagnosis of CMCC.

Treatment

Candidiasis is generally treated with azole antifungals. For some patients, only acute therapy is needed when infections occur. However, for others who have more recurrent disease, prophylactic therapy is necessary to prevent occurrences. One of the most commonly used agents is fluconazole, which is well-tolerated and cost-effective. If patients develop resistance to fluconazole or develop infection despite chronic suppression therapy with fluconazole, other agents may be used. Voriconazole, itraconazole and posaconazole are other more potent agents that may be prescribed. In addition to antifungals, it is important to address endocrine deficiencies. For patients with hypoparathyroidism, serum calcium and magnesium levels need to be monitored and replaced if they are low. Lastly, some CMCC patients, depending on the specific genetic defect, may also have varying degrees of upper- and lower-airway infections, as well as laboratory signs of antibody deficiency, which may require immune globulin replacement therapy.

Diagnosis of CMCC is largely clinical, based on signs and symptoms of presentation.

A Collection of Disorders

CMCC are a collection of disorders that share features of chronic Candida infections in the skin and mucous membranes. Some patients with CMCC have a clearly defined genetic defect. Aside from the candidiasis, depending on their specific underlying genetic defect, many patients have other clinical features such as endocrine disorders and susceptibility to respiratory infections. Due to the heterogeneity of presentation, variable age of presentation and lack of readily available confirmatory laboratory evaluations other than genetic testing, recognition and diagnosis often are delayed and remain a challenge.

BOB GENG, MD, MA, studied medicine at Washington University School of Medicine in St. Louis, where he also completed his residency training in internal medicine. He is currently an assistant professor in allergy and immunology at the University of California, San Diego. Dr. Geng received his bachelor's and Master of Arts degrees in Georgetown University's School of Foreign Service.