An 18-Year-Old Woman With Recurrent Skin, Nail, and Oral Mucosal Abnormalities

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An 18-year-old woman presented to the dermatology clinic for evaluation of recurrent skin, nail, and oral mucosal abnormalities. At age 4 years, she developed white oral plaques that resolved with oral nystatin. Approximately 6 months later, the oral plaques recurred, her toenails became thickened and yellowed, and red plaques appeared on both feet and lower legs. After 3 months of daily oral itraconazole, her skin, nail, and oral mucosal abnormalities resolved for approximately 1 year. Over the following years, she received intermittent 3- to 6-month courses of daily itraconazole for recurrent skin, nail, and oral mucosal abnormalities, which typically recurred within 6 to 12 months of discontinuing itraconazole. Her last dose of itraconazole was approximately 2 years prior to presentation. On physical examination, the patient had white, moist, nonadherent plaques in the oral mucosa and moist red fissures at bilateral oral commissures (Figure, left panel). She also had thickened, yellowed toenails and scaly erythematous plaques on her lower legs and feet bilaterally (Figure, right panel). Results of complete blood cell count with differential were normal, as were results of measurement of serum IgG, IgA, IgM, and IgE levels and analysis of CD3, CD4, and CD8 T-cell subsets. Potassium hydroxide wet mount preparation of skin scrapings from the lower extremities demonstrated fungal elements. Fungal culture of the skin scrapings grew Candida albicans.

Diagnosis

Chronic mucocutaneous candidiasis (CMC)

What to Do Next

C. Restart daily oral itraconazole

The key to the correct diagnosis is recognition that recurrent fungal infections of the oropharynx, skin, and nails are characteristic of CMC. Choices A and B are incorrect because antibiotics and steroid creams are not treatments for candidiasis and may worsen this condition. Although terbinafine (choice D) is an antifungal medication, it is not first-line therapy for CMC.

Discussion

Chronic mucocutaneous candidiasis is a primary immunodeficiency disorder characterized by persistent or recurrent noninvasive infections of the skin, nails, oral cavity, and genital mucosa with Candida species, typically Candida albicans. The differential diagnosis of CMC includes other T-cell deficiency diseases that cause chronic candidiasis such as HIV, severe combined immunodeficiency, CARD9 (caspase recruitment domain-containing protein 9) deficiency, CD25 deficiency, and hyperimmunglobulin E syndrome. Unlike CMC, these conditions are typically associated with invasive Candida infections.
More than half of CMC cases are due to variants in the signal transducer and activator of transcription (STAT1) gene.1,3 Approximately 105 STAT1 gain-of-function (GOF) variants have been reported in patients worldwide.3 Patients typically present with signs and symptoms of CMC at a median age of 1 year and are at increased risk of viral, bacterial, and fungal infections.2 They often have hypothyroidism due to autoimmune thyroiditis and may develop other autoimmune conditions, such as type 1 diabetes, autoimmune cytopenia, and systemic lupus erythematosus.4 Patients with STAT1 GOF variants are at increased risk of cerebral aneurysm and squamous cell carcinoma of the skin and esophagus.5

CMC is also common in patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), which classically presents with a triad of CMC, hypoparathyroidism, and adrenal insufficiency. APECED results from a variant in the autoimmune regulator (AIRE) gene, of which 106 unique variants have been identified.4 A review of 938 patients with APECED reported onset of CMC at a median age of 4 years.6

CMC may also be caused by variants in the genes for IL-17RA, IL17RC, IL-17F, and ACT1, resulting in deficient functioning of IL17-producing T cells.7

The diagnosis of CMC can be made based on characteristic recurrent abnormalities of the skin, nails, and mucosa and by identification of Candida species on fungal culture of skin scrapings or skin biopsy. The definitive laboratory test for diagnosis of CMC is genetic analysis of peripheral blood mononuclear cells to identify a disease-causing variant.

Antifungal treatment with an oral azole medication, such as fluconazole or itraconazole, typically leads to resolution of the skin, nail, and oral mucosal abnormalities in patients with CMC, although clinical response may be delayed if there is extensive skin and nail involvement.8 Chronic suppressive antifungal therapy can prevent recurrences; however, drug resistance frequently develops during long-term therapy.5,8 Fungal drug resistance, which may be less common with intermittent courses of azole treatment, may be treated with azole dose escalation or use of a different azole medication (such as voriconazole or posaconazole).

For patients with STAT1 GOF variants who have severe autoimmune or autoinflammatory diseases, addition of a janus kinase inhibitor, such as tofacitinib or ruxolitinib, has resulted in resolution of CMC.9 These patients should have transaminase levels and complete blood cell counts monitored closely; acyclovir is commonly prescribed for prophylaxis against herpes virus infections because of increased risk of viral infections while taking janus kinase inhibitors.9

Hematopoietic stem cell transplantation has been performed for patients with severe CMC; however, these patients are at high risk of transplant-related mortality. A study of 15 patients with CMC due to STAT1 GOF variants who underwent hematopoietic stem cell transplantation reported an overall survival of only 40% more than 1 year after transplantation.10

Patient Outcome

Whole-exome sequencing identified a heterozygous STAT1 gene GOF variant, confirming the diagnosis of CMC.4 The patient restarted oral itraconazole (400 mg daily), and her mucocutaneous lesions and nail abnormalities improved within 4 weeks and resolved within 3 months. Itraconazole was decreased to 200 mg daily after 3 months of treatment. At her most recent clinic visit 3 months later, the patient had no recurrent clinical manifestations of CMC with itraconazole (200 mg daily).

REFERENCES


