Images in Dermatology

Refractory Phaeohyphomycosis Due to *CARD9* Variants

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A man in his 30s presented with a 9-month history of enlarging, asymptomatic nodules and verrucous plaques on the left cheek. The eruption began as a painless nodule and later developed satellite lesions. It had been excised as a presumed cyst and treated with itraconazole for suspected sporotrichosis, with little improvement. Examination showed coalescent verrucous plaques and nodules with thick, dark-brown crusts on a mildly erythematous base (**Figure 1**). Direct microscopy results showed abundant septate hyphae and yeastlike cells. Histopathologic examination revealed granulomatous inflammation with pigmented septate hyphae in the dermis without sclerotic bodies (**Figure 2**). Fungal culture results yielded slow-growing, olive-gray to black colonies after 2 weeks. Internal transcribed spacer sequencing and phylogenetic analysis identified *Phialophora americana*, a rarely reported melanized fungus.[1]

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Treatment was guided by susceptibility testing and response. Itraconazole plus terbinafine for 4 months produced little improvement. Voriconazole was followed by marked regression after approximately 6 months but was discontinued because of hepatotoxic and phototoxic effects. Posaconazole for 2 months, combined with 3 sessions of 5-aminolevulinic acid photodynamic therapy at 5-day intervals, led to further improvement, leaving mild atrophic scarring. Mild recurrence developed 2 weeks after discontinuation and stabilized after posaconazole was reinitiated. Given the patient's young age, unremarkable medical history, refractory course, and recurrent superficial mycoses, evaluation for an inherited defect in antifungal immunity was pursued. Whole-exome sequencing revealed novel compound heterozygous *CARD9* variants, c.841del (p.Gln281ArgfsTer81), and c.1118G>C (p.Arg373Pro), supporting a diagnosis of *CARD9*-associated immunodeficiency.

Phaeohyphomycosis is caused by melanized fungi and usually involves the skin and subcutis, presenting as nodules, plaques, abscesses, or cystlike lesions that are often on the extremities or face. Diagnosis requires pigmented hyphae or yeastlike elements in tissue, supported by culture and molecular identification.[2] Unlike chromoblastomycosis, sclerotic bodies are absent. Chronic infection may cause progressive local destruction; facial disease can disfigure or extend to adjacent structures, and dissemination, although uncommon, may occur in immunodeficient individuals.

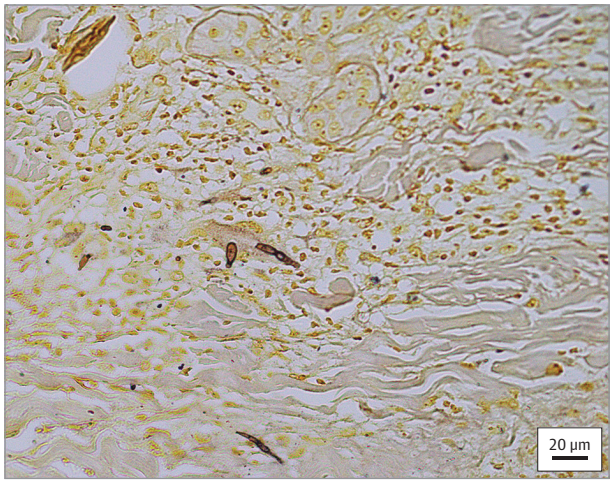
CARD9 is a central adaptor in antifungal immunity downstream of fungal C-type lectin receptors, linking Syk activation to the *CARD9-BCL10-MALT1* complex and subsequent nuclear factor κ light chain–enhancer of activated B cells and mitogen-activated protein kinase–mediated cytokine responses.[3] Impaired *CARD9* signaling compromises T-helper 17–mediated mucocutaneous defense and myeloid-cell fungal clearance, providing a mechanistic basis for the coexistence of long-standing superficial mycoses and refractory subcutaneous phaeohyphomycosis. Clinically, *CARD9* deficiency is characterized by relatively selective susceptibility to fungal infection, including *Candida*, dermatophytes, dematiaceous fungi, and other molds, rather than broad bacterial, viral, or parasitic disease.[4] Other inborn errors of immunity may also predispose individuals to fungal disease but have distinguishing features: *STAT3* deficiency is associated with eczema, elevated immunoglobulin E levels, staphylococcal abscesses, mucocutaneous candidiasis, and mold infection in structurally abnormal lungs;

Figure 1. Clinical Image of Verrucous Plaques on the Left Cheek



Coalescent verrucous plaques and nodules with thick, dark-brown crusting were present on a mildly erythematous base.

Figure 2. Pigmented Fungal Hyphae on Histopathology



Grocott methenamine silver staining (original magnification ×400) showed pigmented septate hyphae in the dermis.

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DOCK8 deficiency with severe cutaneous viral infections, allergy, and cancer risk; chronic granulomatous disease with catalase-positive bacterial infection and invasive aspergillosis; dectin-1 deficiency mainly with mucocutaneous candidiasis; and severe combined immunodeficiency with early-onset multisystem opportunistic infections. Refractory phaeohyphomycosis, particularly in patients with recurrent dermatophytosis or other superficial mycoses, should prompt evaluation for *CARD9* deficiency and may require prolonged triazole therapy with adjunctive surgery or photodynamic therapy in selected cases.[2]

ARTICLE INFORMATION

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