Phaeohyphomycosis caused by Phialophora verrucosa in a patient with CARD9 mutations

Lu Zhang, Yi Zhang, Zijuan Wang, Xiaowen Wang, Ruyu Li
Department of Dermatology and Venereology, Peking University First Hospital, Beijing, China
1Research Center for Medical Mycology, Peking University, Beijing, China
2Beijing Key Laboratory of Molecular Diagnosis on Dermatosis, Beijing, China
3National Clinical Research Center for Skin and Immune Diseases, Beijing, China

Poster session 2, September 21, 2022, 12:30 PM - 1:30 PM

Objective: To study an irritable case of phaeohyphomycosis caused by Phialophora verrucosa and the underlying genetic and immunological mechanisms.

Methods: Clinical and laboratory findings of the patient were studied. The patient’s DNA was sequenced for CARD9. Immunologic and adaptive immunological responses of patient-derived PBMCs were evaluated by ELISA and flow cytometry.

Results: A 29-year-old Chinese male, born to nonconsanguineous parents, developed an enlarging plaque on his right anterior tibia at 23 years and underwent a 15-month treatment of oral itraconazole at the local hospital. Upon discontinuation of the medication, the plaque spread over his face, upper limbs, and back. Physical examination indicated dark-brown verrucous plaques and nodules with surface scales and scales on his right leg, upper limbs, and face. Skin biopsy revealed pigmented yeast cells with budding and yeast cell chains in the dermis. Based on tissue culture, we identified P. verrucosa as the causative pathogen, which was further validated by ITS, SSU, and TEF gene sequencing. Thus, subcutaneous phaeohyphomycosis was diagnosed, and itraconazole combined with amphotericin B was prescribed. The lesions improved only marginally. We, therefore, gave him oral posaconazole instead, based on in vitro antifungal susceptibility results. After 1 month of posaconazole treatment, the serum AST enzyme decreased and the lesions improved markedly.

Based on previous reports linking CARD9 deficiency to phaeohyphomycosis, as well as early onset and recalcitrant characters, Sanger sequencing was performed in this patient and identified two compound heterozygous mutations in exon 6 (R173P) and exon 8 (D274GfsX60) of CARD9. We then evaluated the functional effect of the CARD9 mutations by assessing the stimuli-dependent release of proinflammatory cytokines and helper T cell differentiation. Cytokine production was markedly impaired in PBMCs post 24 h of stimulation with LPS, curdlan, TDB, mannan, MDP, β-glucan, and various fungal ligands. Moreover, the patient showed a significant absence in Th17 and Th22 cell proportions, as well as lower IL-17A and IL-22 production after six days of co-incubation with the stimuli mentioned above.

Conclusion: Our report highlighted that otherwise healthy patients diagnosed with early-onset, unexplained, and recalcitrant phaeohyphomycosis should be analyzed for CARD9 mutations and immune deficiency. Furthermore, posaconazole may be an alternative worth trying after the failure of other antifungals due to its ideal results achieved in our case.