Deep dermatophytosis is a rare form of invasive fungal infection caused by dermatophytes. These ubiquitous filamentous fungi are very common and usually cause superficial benign infection confined to the stratum corneum. In contrast, deep dermatophytosis is characterized by extensive invasion of the dermis and/or lymph nodes with occasional central nervous system dissemination.1-3 Most cases of deep dermatophytosis have been described in individuals from North Africa.4,5 Recently, 17 patients with deep dermatophytosis from Algerian, Tunisian, and Moroccan families were shown to display autosomal recessive deficiency of the CARD9 (caspase recruitment domain 9) protein in a study that identified this genetic defect as the main inherited cause of deep dermatophytosis.6

CARD9, mainly expressed in myeloid cells, is a critical adaptor protein in the signaling pathway downstream from C-type lectin receptors, such as dectin 1, dectin 2, and mincle, involved in the recognition of fungal pathogens.7 As a consequence, cells from CARD9-deficient patients were shown to display impaired proinflammatory cytokine production upon fungus stimulation, impaired neutrophil killing of unopsonized Candida albicans, and/or, for most patients, a decreased proportion of interleukin 17-producing T cells.7

To date, 7 different mutations have been identified in 30 CARD9-deficient patients from 15 families and are present at the homozygous (Y91H,8 R101C,6 p.D274fsX60,9 Q289X,6 and Q295X10) or the compound heterozygous (G72S/R373P11 and p.L64fsX59/p.Q158X9) state. Most were located in the CARD domain (from amino acids 6 to 98) or the coiled-coil domain (from amino acids 140 to 420) and were shown to impair or abolish CARD9 protein expression and function.6 All displayed a selective susceptibility to various superficial and invasive fungal disease, including mucocutaneous candidiasis, dermatophytosis, subcutaneous phaeohyphomycosis, deep dermatophytosis, or Candida species infections of the central nervous system. We herein describe, to our knowledge, the first case of extensive dermatophytosis due to autosomal recessive CARD9 deficiency in an Egyptian patient who was also homozygous for the Q289X allele. Treatment with posaconazole induced a complete remission of the skin and nail symptoms.

Report of a Case

The patient is a man in the fourth decade of life born to an Egyptian family and living in France. The family lived in Gharbeya (northern Egypt) and had no known consanguinity. From 13 years of age, the patient had presented with pruritic dermatosis, beginning with a few erythematous lesions on his hands and lower limbs. He then developed recurrent extensive skin lesions involving the trunk and upper and lower limbs and a nail dystrophy. These lesions worsened 5 years ago with the development of disseminated squamous and keratotic lesions with pruritus and li-
chonification. Clinical examination revealed multiple coalescent, annular, squamous, erythematous, and pigmented plaques scattered on his abdomen, back, gluteal region, and lower limbs. He had nail bed hyperkeratosis and distal onycholyysis of the fingers on the left hand with unusual arcuate lines emerging as a form of proximal subungual onychomycosis (Figure, A). Results of a skin biopsy showed hyperkeratosis and acanthosis of the epidermis; a dermal infiltrate consisting of lymphocytes, eosinophils, and plasma cells; and the presence of hyphae in the epidermis with periodic acid-Schiff reagent staining. Skin scrapings of multiple sites (palms, back, groin, foot sole, and toes) demonstrated the presence of hyphae, and skin cultures yielded *Trichophyton rubrum*. No superficial lymph nodes were found.

Results of chest radiography and abdominal ultrasonography were normal. Hypereosinophilia (0.8×10^9/L) was detected. Results of serologic analysis for human immunodeficiency virus were negative. Levels of T CD4+, T CD8+, B, and natural killer lymphocyte subsets were within reference ranges. He received multiple sequential prolonged courses of antifungal treatment, including systemic itraconazole (200 mg/d for 3 months), ketoconazole (200 mg/d for 3 months), and terbinafine hydrochloride (250 mg, 2 courses in 3 months), as well as topical ketoconazole (+6 months) and ciclopirox olamine (+6 months). Treatment led to some reduction of the lesions and itching. However, chronic lesions always remained, and severe relapses occurred whenever the antifungal drug therapy was withdrawn.

The patient started posaconazole therapy, 400 mg, twice daily (800 mg/d) for 1 month, then 200 mg 3 times a day (600 mg/d) for 2 months (posaconazole blood level, 1.27 mg/L). This 3-month regimen of posaconazole treatment induced a complete clinical remission of skin and nail lesions (Figure, B). Posaconazole therapy was therefore continued for 8 months to allow complete clinical remission.

No severe bacterial, viral, or other fungal infections were reported. The patient’s parents and siblings reported no dermatophytic infections. Using a candidate-gene approach, we sequenced the CARD9 gene (NCBI Entrez Gene 64170) and found a homozygous c.C865T mutation in exon 6 of CARD9, which resulted in a premature termination codon in position 289, Q289X, in the region encoding the coiled-coil domain of CARD9.

Discussion

We described an Egyptian patient with extensive dermatophytosis who is homozygous for the Q289X allele of CARD9, which has been reported previously in North African patients with deep dermatophytosis. The patient described herein had extensive lesions of the skin and nails. However, histologic examination of the skin did not show deep dermatophytic infection per se (no hyphae within the dermis), which emphasizes the phenotypic variability of dermatophytic infection seen in patients with CARD9 deficiency, ranging from extensive skin and nail lesions to potentially lethal lymph node and central nervous system infection. In the setting of extensive or deep dermatophytic infection, patients should first undergo investigation for immunosuppressive drug intake, corticosteroid use, human immunodeficiency virus infection, and lymphopenia. If no risk factor is identified, especially in patients of North African origin with clinical signs starting during childhood, CARD9 deficiency should be investigated. Posaconazole treatment in our CARD9-deficient patient allowed sustained clinical remission, whereas other antifungals with antidermatophytic activity resulted in only partial remission. In the series by Lanternier et al., most patients were treated with griseofulvin, itraconazole, or fluconazole and sometimes with terbinafine, voriconazole, econazole nitrate, liposomal amphotericin B, or ketoconazole. Only 1 patient received posaconazole in addition to several other treatments. Posaconazole is a triazole antifungal drug with potent in vitro activity against dermatophytes. Previous studies demonstrated adequate skin and nail penetration of posaconazole. Posaconazole should be administered orally during a high-fat meal and requires, at high-dosage use (600-800 mg/d), monitoring of blood levels (recommended concentration, 1.2-2.0 mg/L) and liver enzyme levels.

Conclusions

The best treatment for extensive dermatophytosis in the setting of CARD9 deficiency remains to be evaluated. We advise terbinafine as a first-line and posaconazole as a second-line treatment.
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