Posaconazole Treatment of Extensive Skin and Nail Dermatophytosis Due to Autosomal Recessive Deficiency of CARD9

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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-
HC were negative. Levels of T CD4+, T CD8+, B, and natural killer 
lymphocytes were normal. Hypereosinophilia (0.8×10^9/L) was detected. 
Results of serologic analysis for human immunodeficiency vi-
rus were negative. Levels of T CD4+, T CD8+, B, and natural killer 
lymphocytes were normal. Hypereosinophilia (0.8×10^9/L) was detected. 
Results of chest radiography and abdominal ultrasonogra-
phy were normal. Levels of T CD4+, T CD8+, B, and natural killer 
lymphocytes were within reference ranges. He received multiple 
sequential prolonged courses of antifungal treatment, 
including systemic itraconazole (200 mg/d for 3 months), keto-
conazole (200 mg/d for 3 months), and terbinafine hydrochlo-
ride (250 mg, 2 courses in 3 months), as well as topical ketocon-
azole (>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 com-
plete 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 der-
matophytic infections. Using a candidate-gene approach, we se-
quenced 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 dermatophy-
tosis who is homozygous for the Q289X allele of CARD9, which 
has been reported previously in North African patients with deep 
dermatophytosis.6 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 hy-
phae within the dermis), which emphasizes the phenotypic vari-
ability of dermatophytic infection seen in patients with CARD9 
deficiency, ranging from extensive skin and nail lesions to poten-
tially 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 
take, corticosteroid use, human immunodeficiency virus infec-
tion, and lymphopenia. If no risk factor is identified, especially 
in patients of North African origin with clinical signs starting dur-
ding childhood, CARD9 deficiency should be investigated. Posacon-
azole treatment in our CARD9-deficient patient allowed sustained 
clinical remission, whereas other antifungals with antidermato-
phytic activity resulted in only partial remission. In the series by 
Lanternier et al,6 most patients were treated with griseofulvin, 
itraconazole, or fluconazole and sometimes with terbinafine, vori-
conazole, econazole nitrate, liposomal amphotericin B, or keto-
conazole. Only 1 patient received posaconazole in addition to sev-
eral other treatments. Posaconazole is a triazole antifungal drug 
with potent in vitro activity against dermatophytes.12 Previous 
studies demonstrated adequate skin and nail penetration of 
posaconazole.13-15 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 terbi-
nafine as a first-line and posaconazole as a second-line treatment.
ARTICLE INFORMATION

Accepted for Publication: July 3, 2014.
Published Online: November 5, 2014.

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Author Contributions: Drs Jachiet and Bouaziz had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jachiet, Rybojad, Casanova, Puel, Bouaziz.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Casanova.
Obtained funding: Jachiet, Puel.
Administrative, technical, or material support: Casanova.
Study supervision: Bagot, Casanova, Puel, Bouaziz.
Conflict of Interest Disclosures: None reported.
Funding/Support: This study was supported by the Jeffrey Modell Foundation (Dr Puel).

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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