Terbinafine-resistant dermatophytosis in Alabama: two cases of recalcitrant dermatophytosis and the dermatologist's role in detection of drug resistance and antifungal stewardship

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Synopsis:

1. A review of two cases of recalcitrant dermatophytosis which highlight a growing community health concern of antifungal-resistant *Trichophyton* species.
2. Highlight important clinical and diagnostic findings to consider when treating antifungal resistant dermatophytosis.
3. Utilization of fungal culture and antifungal susceptibility testing is imperative to aggressively treat and halt the spread of multidrug resistant tinea, especially for those with recurrent disease..

Introduction

We define recalcitrant dermatophytosis as insufficient response to an adequate antifungal course in a patient with microscopy or culture proven tinea infection.

- New species, including *T. mentagrophytes type viii*, are spreading worldwide, initially from India and now reported in Birmingham, AL.[1]
- Innate terbinafine resistance vs. the widespread use of corticosteroids and topical antifungals in India is theorized to have resulted in *T. mentagrophytes*
- Single nucleotide polymorphisms (SNPs) in the squalene epoxide (SE) gene in *Trichophyton* species leads to terbinafine resistant isolates
- Evolving drug resistant dermatophyte species and lack of new treatments pose an increasing public health burden.[2]
- The minimum inhibitory concentration (MIC) is defined as the lowest concentration of a drug which inhibits microorganism growth.
- The Clinical and Laboratory Standards Institutes (CLSI) has not published standardized guidelines for antifungal resistance in dermatophytes. However, a MIC of >0.5 µg/mL for terbinafine is considered elevated.[3]
  - The break points for itraconazole against *Candida* species are as followed: MIC of ≤0.125 µg/ml is considered susceptible, 0.25 to 0.5 is susceptible dose dependent and greater or equal to 1 is resistant.
  - The break points for fluconazole against *Candida* species are as followed: MIC of ≤8 µg/mL is susceptible, 16-32 µg/mL is susceptible dose dependent and greater or equal to 64 is resistant.[4]

Patient A

24-year-old male with a **5+ year** history of persistent dermatophytosis.

- Exam findings: erythematous scaly plaques with central areas of clearing and active borders on the buttocks, left elbow, right hand, face. (Figure 1.1)
- Social history: lived part-time in India and extensive intercontinental travel history for work
- Prior work-up: previous biopsies showed dermatophytosis. No fungal culture had been sent per medical record review.
- Failed treatments: **several courses of oral terbinafine** prescribed over 5 years.
- On initial exam, skin scraping with KOH was inconclusive. Fungal culture was sent and grew *T. mentagrophytes type viii.*
- Speciation and susceptibility reported in **Table 1** highlighting terbinafine resistance.
- Patient was treated with fluconazole 200 mg daily, econazole 2% cream, & ciclopirox shampoo.

Figure 1.1 Patient A: buttocks and left shoulder

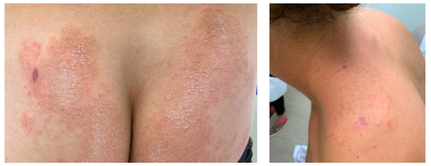

Figure 1.2: Fungal culture growing *T. mentagrophytes type viii* on potato agar

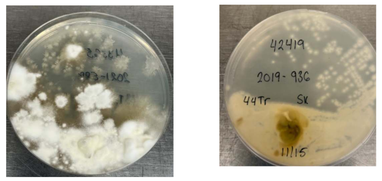

Table 1. Susceptibility Report with Minimum Inhibitory Concentrations (MIC) (µg/mL) for Patient A highlighting *T. mentagrophytes* resistance to terbinafine

Susceptibility Report: Trichophyton mentagrophytes	
Antifungal	*MIC in µg/mL:*
Fluconazole	= 8.0
Itraconazole	= 0.25
Terbinafine	> 0.5
Method: CLSI M38A3 microdilution	

Table 2: MIC (µg/mL) and FICI Results of *T. mentagrophytes* against Itraconazole, Fluconazole and Combination of Itraconazole and Fluconazole.

	Itraconazole [16]-A	Fluconazole [64]-B	Itraconazole [16]-A*+ Fluconazole [64]-B*
Trichophyton mentagrophytes	A= 0.125	B= 16	A*= 0.008, B*= 0.250
FICI = A*/A + *B/B = 0.008/0.125 + 0.250/16 = 0.064 + 0.015 = 0.079			
FICI = 0.076 < 0.5 = Synergistic Interaction			

Patient B

46-year-old male with a **10+ year** history of recalcitrant dermatophytosis.

- Exam findings: erythematous scaly coalescing papules and plaques with active erythematous borders on the posterior thighs, abdomen, buttocks (Figure 2.1)
- Prior failed treatments: terbinafine, itraconazole, fluconazole without improvement.
- Fungal cultures grew *T. rubrum,* **Figure 2.2**
- Speciation and susceptibility: reported in **Table 2** revealed terbinafine, itraconazole, and fluconazole resistance. Posaconazole and griseofulvin susceptible.
- Additional failed treatment: griseofulvin 250 mg three times daily x 3 months
- Secondary treatment: Posaconazole 300 mg daily x 6 weeks.

Figure 2.1 Patient B: lower abdomen and posterior thighs

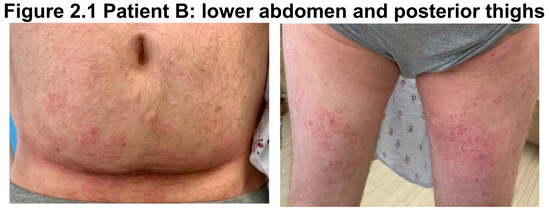

Figure 2.2: Fungal culture growing *T. rubrum* on potato agar

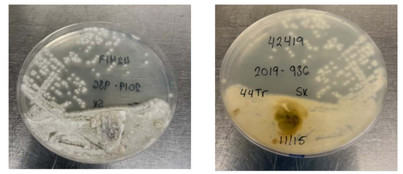

Table 2. Susceptibility Report with Minimum Inhibitory Concentrations (MIC) (µg/mL) for Patient B highlighting *T. rubrum* resistance to terbinafine, itraconazole, and fluconazole (2019-936).

Susceptibility Report: Trichophyton rubrum	
Antifungal	*MIC in µg/mL:*
Amphotericin B	= 1.0
Ciclopirox	= 1.0
Fluconazole	> 16
Griseofulvin	= 2.0
Itraconazole	> 8.0
Posaconazole	= 0.25
Terbinafine	> 0.5
Voriconazole	= 0.25
Method: CLSI M38A3 microdilution	

Current Systemic Antifungal Treatment Options

- Terbinafine 250 mg daily
- Fluconazole 200 mg daily
- Itraconazole 200 mg daily
- Griseofulvin (ultramicronized) 300-375 mg/daily
- Posaconazole (off-label) 300mg daily

**Add topical antifungals from a different class. If oral azole- use topical allylamine (terbinafine) or ciclopirox.

Conclusion

There is a growing concern regarding the increase in the incidence of resistance development of dermatophytes against terbinafine.

The presented cases illustrate the growing epidemiological trend of antifungal- resistant dermatophytosis in the US.

These cases illustrate the growing epidemiological trend of antifungal- resistant dermatophytosis. This warrants a change in dermatologists' clinical practices to 1) consider drug resistance in recalcitrant cases of dermatophytosis 2) evaluate the utility of fungal culture and interpreting antifungal susceptibility testing to isolate resistant species 3) practice antifungal stewardship and treat aggressively.

References

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