

Clinical Characteristics and Pattern of Use of Topical and Oral Antifungal Drugs in Recalcitrant Dermatophytosis: A Hospital-Based Study

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ABSTRACT

Introduction

Studies on clinical characteristics of recalcitrant dermatophytosis from Nepal are sparse. The objective of this study was to characterize recalcitrant dermatophytosis clinically and to see pattern of use of existing antifungal drugs in these patients.

Methods

This was a prospective observational study carried out in Department of Dermatology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal for a period of one year (December 2022 through November 2023). All the cases of recalcitrant dermatophytosis who visited Dermatology outpatient department during this period were included in this study. The study variables included age, sex, occupation, site of involvement, prior use of topical drugs, oral terbinafine and oral itraconazole. Descriptive analysis of data was done using frequencies and percentages.

Results

Out of sixty cases of recalcitrant dermatophytosis, there were 32(53.3%) females and 28(46.7%) with mean age 34.47(SD +/- 11.96). Plaque (75%, n=45) presentation was the commonest type followed by annular (15%, n=9), polycyclic (6.7%, n=4), and patch type (3.3%, n=2). Multiple sites were involved in 35 patients (58.3%). Most of the patients had used topical corticosteroids (36.7%, n=22) at presentation. Sixteen patients had history of use of oral drugs prior to presentation without any improvement; Itraconazole (23.3%, n=14) was the most common drug used, followed by Terbinafine (1.7%, n=1).

Conclusion

Plaque type of recalcitrant dermatophytosis in young female with multiple sites of involvement was the most common presentation. Many patients had used topical corticosteroid and topical antifungals while majority had never used oral drugs prior to presentation in hospital.

Keywords

Antifungals; dermatophytes; infection

INTRODUCTION

Cutaneous fungal infections, particularly dermatophytosis also called tinea, are common superficial fungal infections affecting 20-25% of global population, with rates as high as 40-60% in areas of high prevalence.¹ In 2017, fungal infections were the most common skin disease globally affecting 750 million people across both sexes.² In Nepal, the prevalence of dermatophytosis varies geographically, ranging from 11.4% in southern region bordering India to 0.9% in northern hilly areas.³ Clinically, tinea typically presents as annular erythematous papules, plaques or papulovesicular lesions with central clearing depending on infecting pathogens.

Recalcitrant tinea or difficult-to-treat tinea refers to chronic, relapsing, or recurrent infections with various clinical presentations reported worldwide.⁴ In India, the prevalence of recalcitrant tinea infections is around 62.5%.⁵ A study conducted in Nepal involving 349 patients identified *Trichophyton rubrum* as the most common organism in contrast to *Trichophyton mentagrophytes*, which is frequently associated with recalcitrant tinea in neighboring India.^{5,6}

In Nepal, topical and systemic antifungal drugs, fixed drug combination of antifungals with steroids and topical steroids are easily available over the counter and are often misused.⁷ This misuse may contribute to the development of recalcitrant dermatophytosis. As this pattern has not been previously documented in Nepal, the present study was undertaken to examine the clinical patterns of recalcitrant tinea and evaluate the use of topical and systemic antifungal treatments among the affected patients in our settings.

METHODS

This was a prospective observational study carried out in department of dermatology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal for a period of one year (December 2022 through November 2023). Non-probability convenience sampling was used for collection of cases. Recalcitrant dermatophytosis for this study was defined as persistent tinea like chronic (more than 6 months duration), recurrent (reoccurrence of disease within 6 weeks of completion of treatment), corticosteroid-modified, and resistant cases, with poor or no response to standard treatment.

All the doctors responsible for consultation of patients in the Outpatient Department of Dermatology of Tribhuvan University Teaching Hospital were informed about the research on recalcitrant dermatophytosis and were asked to refer suspected cases to principal investigator and the team for reevaluation of the cases. These cases

were again examined by the team for fulfillment of criteria of recalcitrance and were subjected to potassium hydroxide (KOH) examination.

Skin scraping was taken with the help of number 15 blade from the active lesions in a glass slide and covered with a cover slip. 20% KOH drop was put at the edge of coverslip and kept for 20 minutes for dissolving the keratinocytes and examined by microscope under 10X for presence of branching hyphae. Only those cases who were KOH positive and fit the definition of recalcitrant dermatophytosis were included in this study. The study variables included age, sex, morphology of lesions, occupation, site of involvement, prior use of topical drugs, oral terbinafine and oral itraconazole. All these data were recorded using preformed proforma.

All the data were recorded in excel sheet first and then transferred to SPSS 27 for analysis. Descriptive analysis of the data was done and expressed using frequencies, percentages, and mean. The study was approved by the institutional review committee of Institute of Medicine, Tribhuvan University, Kathmandu, Nepal (Ref no: 629(6-11) E2).

RESULTS

Sixty cases of recalcitrant dermatophytosis were enrolled in this study period. The mean age of the patient in this study was 34.47 years (SD +/- 11.96) with 32 (53.3%) females and 28 (46.7%) males. Housemakers (n=17), and students (n=16) were the most common occupational group affected by recalcitrant tinea infection. The commonest clinical presentation was plaque type (75%, n=45) (Table 1).

Table 1. Clinical presentation of recalcitrant dermatophytosis

Type	Frequency (%)
Patch	2 (3.3%)
Plaque	45 (75%)
Annular	9 (15%)
Polycyclic	4 (6.7%)
<i>Total</i>	<i>60 (100%)</i>

Single site was involved in 25 patients (41.7%) whereas multiple sites were involved in 35 patients (58.3%). Sixteen patients had history of use of oral drugs prior to presentation without any improvement; Itraconazole (23.3%, n=14) was the most common drug used, followed by Terbinafine (1.7%, n=1) and multiple drugs (1.7%, n=1) (Table 2).

Table 2. Patterns of oral treatment

History of prior treatment with antifungals	Frequency (%)
No treatment	44 (73.3%)
Itraconazole	14 (23.3%)
Terbinafine	1 (1.7%)
Multiple drugs	1 (1.7%)
<i>Total</i>	<i>60 (100%)</i>

Most of the patients (n=55) had history of use of topical treatment prior to the presentation and included topical corticosteroids (36.7%, n=22) in majority (Table 3).

Table 3. Patterns of topical treatment

Previous topical treatment	Frequency (%)
No treatment	5 (8.3%)
Topical antifungals	21 (35%)
Topical corticosteroids	22 (36.7%)
Combination	12 (20%)
<i>Total</i>	<i>60 (100%)</i>

DISCUSSION

In this study of 60 cases of recalcitrant dermatophytosis, the most common clinical presentation was plaque type (75%), followed by annular (15%), polycyclic (6.7%), and patch type (3.3%). Recalcitrant tinea was first described in a Nepalese patient in Japan. Phylogenetic analysis identified the causative organism as *Trichophyton mentagrophyte* type VIII, later designated as *Trichophyton Indotineae*. This organism was responsible for unusual clinical presentations and resistance to terbinafine.⁸

According to reports from India,⁹ a new species *Trichophyton Indotineae*, is responsible for causing recalcitrant dermatophytosis in Indian subcontinent. The clinical manifestations of this infection include widespread inflammatory lesions involving the groin, gluteal region, trunk, and face affecting individuals of all genders. In a study by Tamimi et al, infection with *Trichophyton Indotineae* was associated with longer duration of disease.¹⁰ Another study from Israel described recalcitrant dermatophyte infections as extensive, large, erythematous annular plaque primary involving the groin, perineum and buttocks.¹¹ In our study, multiple sites involvement was seen in majority of cases (58.3%) which is similar to those described for recalcitrant dermatophytosis from previous

studies.^{4,9,11} Although *Trichophyton Indotineae* is the primary species implicated in most recalcitrant cases, other dermatophyte species have been reported as causative agents.¹⁰

In this study, out of all cases of recalcitrant dermatophytosis, it was seen that majority of patients (n=22, 36.7%) had applied topical steroid (monotherapy) prior to presentation, followed by antifungals (n=21, 35%), combination i.e. steroid mixed with antifungal, and antibiotics (n=12, 20%), and 8.3% (n=5) developed recalcitrance without application of any topical drugs. It shows that the recalcitrance may be related to use of topical steroid in majority of cases, but the organism might have developed resistance in community to commonly used antifungals and because of emergence of intrinsic resistance. Similar findings were noted in cases of use of oral drugs in this study. There were cases of dermatophytosis resistant to itraconazole in majority (23.3%, n=14), terbinafine (n=1) and multiple drugs (n=1). The result seems to be completely different from the cases of resistance reported to terbinafine worldwide.⁸⁻¹⁰⁻¹¹ In a study in Nepal, 274 patients dermatophytosis were evaluated for mycological profile and antifungal sensitivity pattern.¹² It was seen that *Trichophyton* spp was commonest cause of infection followed by *Microsporum* spp and they were still susceptible to itraconazole and terbinafine. This contrast to our finding of recalcitrant dermatophytosis where the patients were not responding to itraconazole and terbinafine. It can be thus made out that majority of dermatophytosis still responds to itraconazole and terbinafine in our part of the world but resistance to treatment with itraconazole and terbinafine is rising as seen in our study on recalcitrant cases.

Terbinafine resistant species have been seen in studies from the Indian subcontinent and globally, primarily attributed to *Trichophyton Mentagrophytes* ITS genotype VIII.^{9,13-16} In addition to terbinafine, itraconazole resistance is an emerging concern, as demonstrated in a European study.¹⁷ In this study, Saunte et al, collected data via questionnaire from twenty European countries and found 96 cases of dermatophytes resistant to commonly used antifungal agents. While terbinafine resistance was most frequently reported, resistance to itraconazole, fluconazole, and griseofulvin was also documented. Contrary to the global trend of predominant terbinafine resistance, our study observed treatment resistance with itraconazole. This finding warrants further confirmation through antifungal sensitivity testing, molecular species identification of species and the resistance gene analysis in the local context.

Recalcitrant dermatophytosis may arise from both clinical and mycological factors.¹⁸ Clinical resistance is defined as a lack of response despite

appropriate dosing and duration. This may result from host-related factors (e.g. immunosuppression, comorbidities like diabetes), disease- factor (e.g. severity, chronicity), or and treatment-related issues (e.g. non-compliance, low drug bioavailability). Additionally, inappropriate therapy and polypharmacy can contribute to poor outcomes.

Mycological resistance may be either primary (intrinsic) or secondary (acquired). Primary resistance involves genetic mutation present before drug exposure and includes naturally resistant *Trichophyton* species. Secondary resistance refers to acquired point mutations, such as in squalene epoxidase gene(linked to terbinafine resistance) and the ERG11 genes (associated with azole resistance).¹⁸

The problem of recalcitrant dermatophytosis in Nepal mirror trends in nearby countries, including India⁵, Srilanka¹³, Bangladesh and China.^{19,20} Although molecular characterization of the dermatophyte was not performed in this study, the observed treatment resistance patterns suggests the presence of multi-drug-resistant strains in our setting. This study points toward possible resistance to azoles, allylamine and calls for newer effective drugs for overcoming treatment resistance in present context. One limitation of this study is the lack of assessment of patient compliance, which may have influenced treatment outcomes. Future studies should include detailed evaluation of adherence to treatment protocols. We strongly recommend molecular studies and antifungal susceptibility testing in future research to confirm these observations and guide effective management strategies.

CONCLUSION

Recalcitrant dermatophytosis in this study predominantly affected young females, with multiple site involvement and plaque- type lesions being the most common presentation. The findings suggest the emergence of multi-drug resistance and possible de novo resistance mechanisms, differing from previous studies that primarily report terbinafine resistance. We therefore recommend future research focused on molecular or phylogenetic characterization of pathogens and careful assessment of compliance to confirm these observations and guide effective management strategies.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

UP contributed substantially to concept, design, literature review and manuscript preparation. SP contributed to data collection, data analysis, statistical analysis and manuscript preparation.

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