Original Article

Isolation of dermatophytes associated with patients of tinea corporis not responding to standard terbinafine treatment protocol

Neha Sharma[1*], Uma Tendolkar[2]

[1]Speciality Medical Officer, [2]Professor(Retired), Department of Microbiology, Lokmanya Tilak Municipal Medical College, Sion, Mumbai.
Email: dr.neha1986ak@gmail.com

Abstract

Background: Dermatophytoses is a superficial fungal infection of keratinized tissue. Oral terbinafine is effective in the treatment of superficial dermatophyte infections, generally achieving cure in > 80% of patients.The occurrence of terbinafine resistant clinical isolates is rare one case has been documented and with abnormally low susceptibility to terbinafine do exist. Hence, this study was undertaken to isolate dermatophytes associated with patients of tinea corporis not responding to standard terbinafine treatment protocol. **Material and Methods:** A total of the 187 cases were clinically diagnosed as tinea corporis.The skin scrapings were collected two times from each patient, before instituting treatment and one week after completion of terbinafine treatment in clinically resistant cases. **Results:** In 64 (34.2%) patients with *T. rubrum* and *T. mentagrophytes* infections were resistant to treatment with terbinafine. Patients had persistent lesions and all these were positive by direct microscopy or culture or both in their post treatment clinical specimens. **Discussion:** Treatment of cutaneous dermatophytosis has increasingly become difficult. Among various options, topical terbinafine for 4 weeks appears to be the treatment of choice. However, an appropriate dose and duration of administration which can produce mycologic cure and prevent recurrence remains elusive.
Key Words: Dermatophytoses, Tinea corporis, Terbinafine, Resistance.

[*]**Address for Correspondence:**
Dr. Neha Sharma, Department of Microbiology, Lokmanya Tilak Municipal Medical College, 4th floor College Building, Sion, Mumbai.
Email: dr.neha1986ak@gmail.com
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INTRODUCTION

Dermatophytoses is a superficial fungal infection of keratinized tissue, caused by keratinophilic fungi called dermatophytes. Dermatophytoses is commonly called as tinea. Tinea corporis is the dermatophytoses of glabrous skin[1]. Many topical antifungals of different groups are available for the treatment of dermatophytoses such as azole derivatives, allylamines, benzylamines, morpholine, etc., Systemic drugs, such as terbinafine and itraconazole, are currently used for the treatment of severe and chronic dermatophytosis[2]. Terbinafine is very widely used both orally and topically, in therapy of dermatophyte infection[3]. Terbinafine hydrochloride is one of the fungicidal allylamine groups of drugs with broad spectrum of antifungal activity. It interferes with fungal sterol biosynthesis at an early stage. It also inhibits squalene epoxidation, leading to intracellular accumulation of toxic squalene responsible for fungal cell death[3]. Oral terbinafine 250 mg/day is effective in the treatment of superficial dermatophyte infections such as onychomycosis, tinea pedis and tinea corporis/cruris, generally achieving mycological cure in > 80% of patients. The drug is also effective in children with tinea capitis when administered orally in the dosage range 62.5 to 250 mg/day for 4 weeks[4]. The occurrence of terbinafine resistant clinical isolates is rare one case has been documented and thoroughly investigated. Nevertheless dermatophytes with abnormally low susceptibility to terbinafine do exist[5]. Hence, this study was undertaken to isolate dermatophytes associated with patients of tinea corporis not responding to standard terbinafine treatment protocol.

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MATERIAL AND METHODS

The present prospective study was carried out in the Department of Microbiology, over a period of one year. A total of 187 clinically diagnosed and culture positive cases of tinea corporis infection of all age groups of both sexes were taken for the study. After the detailed history, a detailed clinical examination of patient was done. The affected area was swabbed with 70% alcohol and the active edge of lesion scraped with a sterile scalpel. The scrapings were collected from the margins of the lesion without injuring the skin surface. The scrapings were collected in a sterile petri dish. The skin scrapings were collected two times from each patient, before instituting treatment and one week after completion of terbinafine treatment (Terbinafine treatment 250 mg orally daily for minimum 2 and maximum 4 weeks). The samples were examined for dermatophyte hyphae, arthroconidia by using 10% KOH. Specimens were then cultured on Sabouraud's Dextrose Agar (Merck, Germany) containing Chloramphenicol, Gentamycin and Cyclohexamide; and were kept at 26°C for four weeks. fungal growth was identified by slide culture and physiological and biochemical tests[1].

RESULTS

A total of the 187 cases were clinically diagnosed as tinea corporis. The maximum number of patients 66 (35.3%) were found in the age groups of 21 – 30 years. There were 109 males and 78 females showing more prevalence in males. The study included patients who were positive for dermatophyte culture. It was observed that 64 patients were clinically resistant to antifungal treatment. *T. rubrum* was isolated from 136 patients (72.7%) and *T. mentagrophytes* from 51 (27.3%). Among 136 patients with *T. rubrum* infection, 44 (32.4%) were resistant to treatment, whereas, 20 (39.2%), out of 51, *T. mentagrophytes* infected patients were resistant (Table 1).There was no significant difference in the species isolated from responsive group and resistant group. The clinically resistant patients were 64 out of 187 (34.2%).

Table 1: Culture results in Terbinafine resistant cases

Total no. of culture positive patients (n=187)	Terbinafine Resistant cases (n=64)		Total	
	No.	%	No.	%
T. rubrum (N=136)	44	32.4	136	72.72
T.mentagrophytes (N=51)	20	39.2	51	27.28
Total	**64**	**34.2**	**187**	**100**

Table 2: Comparison of Age between Terbinafine resistant cases

Age (yrs)	Terbinafine Resistant cases (N = 64)			Total (N = 187) No.(%)
	T.rubrum (N = 44) No.(%)	*T.mentagrophytes* (N = 20) No.(%)	Total No. (%)	
≤ 20	06(*13.6*)	03(*15.0*)	09(*04.7*)	27(*14.4*)
21 – 30	16(*36.3*)	06(*30.0*)	22(*62.5*)	66(*35.3*)
31 – 40	05(*11.4*)	07(*35.0*)	12(*29.7*)	48(*25.7*)
41 – 50	12(*27.3*)	03(*15.0*)	15(*03.1*)	35(*18.7*)
> 50	05(*11.4*)	01(*05.0*)	06(*03.1*)	11(*05.9*)
Total	**44**	**20**	**64**	**187**

The highest 79.7% of patients were in the age group of 21-50 years (149/187). Lesser number of patients were seen in age group <20 years and > 50 years. A total of 66 (35.3%) terbinafine resistant cases were between age group of 21-30 years. Out of these 66, 16 (36.6%) were T. rubrum and 6 (30%) were of T. mentagrophytes (Table 2).

Table 3: Gender distribution between Terbinafine resistant cases

Gender	Terbinafine Resistant cases (N = 64)			Total (N = 187) No.(%)
	T.rubrum (N = 44) No.(%)	T.mentagrophytes (N = 20) No.(%)	Total No.(%)	
Male	32(*72.7*)	10(*50*)	42(*65.6*)	109(*58.3*)
Female	12(*27.3*)	10(*50*)	22(*34.4*)	78(*41.7*)
Total	**44**	**20**	**64**	**187**

In terbinafine resistant cases, there was a predominance of males 65.6% as compared to females 34.4% and the difference was not significant (Table 3). In the patients infected with *T. rubrum*, 9 out of 44 patients (20.4%) showed severe lesions which was higher than seen in the responsive group in whom only 5 out of 92 (5.4%) showed severe lesions. Thus, the severity of lesions in resistant cases due to *T. rubrum* infection was significantly high. While in patients with *T. mentagrophytes*infection, the type of lesions were mild or severe was observed in resistant groups. It was seen that in 10 out of 20 (50%) resistant cases, the lesions were severe. The severity of lesions in resistant cases was significantly higher than in responsive cases. Multiple lesions were seen in both responsive and resistant group but difference was not significant. Multiple sites were affected in some of the 187 patients. It was observed that 25% of the patients in the resistant group with *T. rubrum* infections had lesions on face as compared to 9.8%of the patients in the responsive group and the difference was significant indicating that T.faciae caused by *T. rubrum* was more likely to be resistant than responsive. Abdomen was the commonest site of infection in both groups, followed by back. Face was the least commonly affected site. 25% of the cases among *T. rubrum* Resistant group had lesions on face. Among *T. mentagrophytes*20%Resistant group had lesion on face but the difference was not significant. All the 187 patients of tinea corporis had typical signs and symptoms of scaling, raised border of lesion and itching. Papulovesicular rash and pain were complained by 3.7% of patients. Satellite lesions were observed in 4.8% of patients. 100% of the cases had Erythema among *T. rubrum* Responsive group and *T. rubrum* Resistant group which were same and difference was not significant. 96.8% of the cases had Erythema among *T. mentagrophytes* Responsive group which was comparable to 95% of the cases among *T. rubrum* Resistant group and difference was not statistically significant. There was no statistically significant difference in the signs and symptoms of *T.rubrum* infection and *T.mentagrophytes* infections, so also, among resistant groups. After the completion of the antifungal therapy, repeat mycological assessment was done by collecting scrapings for microscopy and culture. In *T.rubrum* infected patients KOH positivity was seen in 31 out of 44 patients who were clinically resistant (70.45%). Culture was positive in all the 43 patients. Only KOH positivity with culture negativity was seen in one patient. A total of 20 patients infected with *T. mentagrophytes* were resistant to antifungal treatment. In these, KOH positivity was seen in 15 (75%) and culture was positive in18 (90%) patients. Thus, in all the 20 patients either microscopy or culture or both were positive even after end of treatment.

DISCUSSION

Although there are few studies to suggest that antifungal resistance is not common in tinea capitis, such data are lacking with respect to tineacorporis. This should also be seen with respect to the currently prevailing clinical scenario in India where there is an increasing recognition of a rising trend of nonresponsive cutaneous dermatophytosis[6,7]. The treatment of Tinea corporis involves use of topical antifungal creams and Terbinafine is the latest addition to the antifungal armamentarium. Following oral administration of terbinafine for treatment of Tinea corporis a clinical cure rate of 71–100% has been reported[8]. In our study, out of 187 patients studied 123 responded clinically favourable to treatment (65.8%) and 64 did not respond clinically to treatment (34.2%). Thus, the clinical cure rate was little less than reported by Newland *et al*[8]. Despite the extensive use of terbinafine for treatment of dermatophytosis, the first clinically confirmed case of resistance to terbinafine in dermatophytes was reported in 2003[9]. Most of the studies indicate that Terbinafine resistance is encountered in *Trichophyton rubrum* whereas *Trichophyton mentagrophytes*has not been studied for its Terbinafine resistance. In our study which included only culture positive Tinea corporis patients, *T.rubrum* and *T.mentagrophytes* were the species isolated from 72.7% and 27.3% patients respectively. Thus, our findings were in conformity with other authors[10,11]. In a recent study, 71 culture positive cases of T.corporis was studied and the fungal isolates were *T.rubrum* in 59 (83%), *T.mentagrophytes* in 10 (14%) and *Epidermophytonfloccosum* in 2 (3%)[10]. In another study, culture results of 50 cases of tinea corporis revealed *T.rubrum* in 33 (66%) and *T.mentagrophytes* in 17 cases (34%)[11]. Most of the reports published so far from India unequivocally report *T.rubrum* to be the commonest dermatophyte isolated from various types of dermatophytosis followed by *T.mentagrophytes*[12]. Tinea corporis is the commonest clinical presentation of dermatophytosis as shown by several authors[10,11,13]. In our study we found that 32.4% of patients infected with *T. rubrum* and 39.2% of patients infected with *T. mentagrophytes* were clinically resistant to treatment but this difference was not significant. In our study, no age related significant difference was found in resistant and responsive patients so also between *T. rubrum* and *T. mentagrophytes* infected patients.In the report of terbinafine resistant *T. rubrum*[14], 6 sequential clinical isolates of *T. rubrum* from a single patient who failed the therapy on oral terbinafine were found to be resistant to

terbinafine in vitro. At present very little is known concerning drug resistance mechanisms in dermatophytes. It is suggested that since Terbinafine resistant T.rubrum isolates are cross resistant to other classes of squalene epoxidase inhibitors. It is suggested that resistance is associated with changes in target enzymes rather than over expression of efflux pumps[14]. The maximum number of lesions were >9 found in 9.4% of resistant group. Persistence of symptoms though was observed in the resistant group even after complete treatment.It was observed that in our study, after completion of antifungal treatment, 64 patients still complained of persisting symptoms like pruritis. All these patients infected with *T. rubrum* (44) and *T. mentagrophytes* (20) were positive in direct microscopy or culture or both, when repeat assessment was done post treatment. Treatment of cutaneous dermatophytosis has increasingly become difficult. Among various options, topical terbinafine for 4 weeks appears to be the treatment of choice for limited disease (tinea corporis/cruris/pedis). For more extensive disease, the choice is less clear.However, an appropriate dose and duration of administration which can produce mycologic cure and prevent recurrence remains elusive.

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