Original Article

Diagnosis of a recurred lesion in dermatophytosis patients after 2 weeks of antifungal therapy: A prospective observational study

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Abstract

Few researchers believe that various risk factors may complicate the course of dermatophytosis and/or develop various dermatoses unrelated to fungal infection at the previous lesion site. However, there is a paucity of studies that analyzed the diagnosis of lesions that recurred at the treated site of dermatophytosis. **Materials and Methods:** A prospective observational study was conducted on 157 cases of dermatophytosis with positive fungal test results. A fixed dose of 100 mg of oral itraconazole once daily was administered to all patients for 2 weeks. At the end of 2 weeks, patients were assessed for clinical cure and recurrence. Recurred cases were assessed for mycological profile using a fungal test (potassium hydroxide mount and/or fungal culture) for identifying fungal infection. **Results:** Only eight (5.36%) patients showed clinical cure, and 141 (94.63%) patients developed recurrence after therapy. Of the 141 cases with recurrence, only 47 (33.33%) patients were positive for fungus. Eight (5.09%) patients were lost to follow-up. Frequently encountered risk factors in the study were topical steroid use, disease in family, associated atopic dermatitis and contact with pets. **Conclusion:** This is the first study that described the clinical diagnosis and mycological profile of the various lesions recurring at the previous tinea infection site in patients with dermatophytosis. Such patients presented not only with recurrent lesions of fungal infection but also developed various dermatoses unrelated to fungal infection at the sites of previous tinea infection. Various factors, which could have resulted in the observed changes, are reinfection by dermatophytes at the sites of previous tinea infection, inadequate antifungal therapy or antifungal resistance; or due to the effects of various topical steroid formulations used by the patients, such as anti-inflammatory or immunosuppressive effects or shift in immunity. Hence, diagnosis of the recurrent lesion at the site of previous dermatophytosis must be individualized and should be based on 1) duration of antifungal therapy received, 2) associated risk factors, 3) response to antifungal therapy, 4) evolution of the recurrent lesion, and/or 5) fungal tests.

Keywords: Complicated dermatophytosis, post-traumatic eczema, reurrent dermatophytosis, risk factors, topical steroid withdrawal

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Introduction

Recent studies reported a rise in the prevalence of recurrence at the treated site of dermatophytosis.[1-6] However, despite extensive research, diagnosis of recurred lesions at the treated

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site of dermatophytosis has become a challenge for physicians. Recently, few researchers reported that dermatophytosis patients may develop various lesions such as complicated/drug-resistant tinea, adverse effect unique to prolonged topical steroid use ("topical steroid withdrawal syndrome"), and chronic eczema/post-traumatic eczema at the previous sites of dermatophytosis.[1,6-19] Further, it is interesting to note that researchers did not find any correlation between risk factors like fungal infection of nail and disease in family members with the chronic dermatophytic infection.[20-22] Hence, it is important for physician to appropriately diagnose the recurrent lesions at the treated site of dermatophytosis prior to initiating therapy.

The present study analyzed the treatment outcome and diagnosis of the recurrent lesions at the treated site of dermatophytosis using fungal test (KOH and fungal culture).

Study type

A prospective observational study was conducted at the tertiary care hospital of eastern India, from June 2017 to May 18. Patients were enrolled after obtaining an ethical approval from institutional ethics committee (IEC Approval Letter No-IEC-T/IM-F/DERMA/15/25), and prior informed consent from patients.

Materials and Methods

A total of 157 consecutive patients suffering from dermatophytosis with positive fungal test, aged above 12 years and both gender, who did not receive topical antifungals in last 1 month and oral itraconazole in last 3 months were enrolled. Patients having comorbidity (diabetes, HIV infection and hypothyroidism), aged above 70 years, on immunosuppressive drugs (corticosteroid and cytotoxic drugs in last 4 weeks), associated fungal infection of nail and hair, pregnant, and lactating women were excluded. Enrolled patients were assessed for risk factors, course of disease (number of recurrences, and response to antifungal therapy), duration of symptom free period prior to recurrence, total duration of the disease, duration of antifungal drugs received, and morphology of lesion at baseline using a predesigned proforma.

All enrolled patients were prescribed oral itraconazole 100 mg capsules once daily for 2 weeks.[23] Patients also used topical luliconazole 1% cream twice daily, and tablet cetirizine 5 mg daily (max 10 mg). At the end of 2 weeks, patients were assessed for clinical cure (i.e. disappearance of signs, and symptom with/without the postinflammatory pigmentation) and recurrence (i.e. partial response, no response, aggravation, and/or recurrence after a brief period of clinical cure). Patients with recurrent lesions were subjected to tests for fungal elements such as KOH mount and fungal culture for diagnosis and identification of the cause. [Flow chart]

Sample size

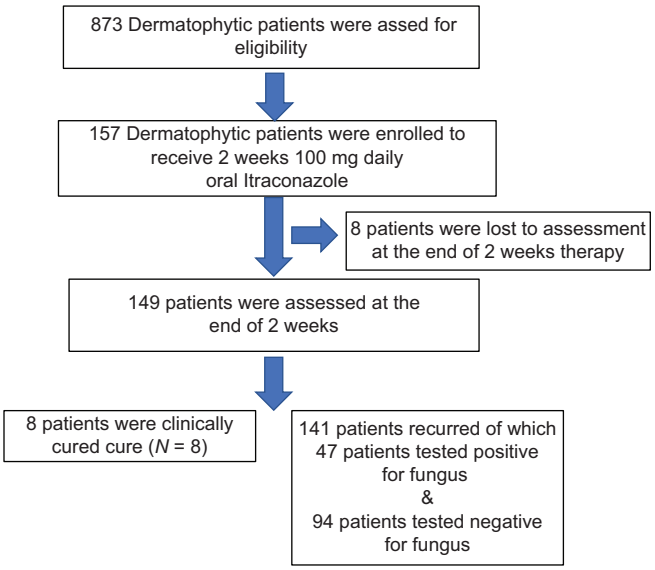
With the anticipated frequency of the outcome factor in the population of 50% ±5, and population size as 10,00,000, confidence level as 80% and design effect of 1, a sample size of 165 patients was estimated.

Statistical analysis

The statistical analysis was done in two parts. The descriptive data were expressed as frequency or proportion. The numerical or quantitative data were expressed as mean ± standard deviation and median. Chi-square test was used for test of statistical significance between the groups.

Result

Eight hundred and seventy-three patients of dermatophytosis who attended the dermatology OPD during the study period were screened. Of these patients, one hundred and fifty-seven (17.98%) patients fulfilled the study criteria and were administered 100 mg oral itraconazole for 2 weeks. The demographic details of the enrolled patients are enlisted in Table 1. The mean age of patients was 32.26 years (range 12–61 years). Male to female ratio was 2:1 (male 104 (66.24%), female 52 (33.12%), and transgender 1 (0.63%)). One hundred and seventeen (74.5%) patients had more than one clinical types of tinea lesions (based on the site involved). The median duration of disease was 3 months (range 1–12 months), median symptom-free period prior to recurrence at enrolment was 06 days (range 0–32 days), and median number of recurrences experienced by the enrolled patients was



Flow chart: Flow chart describing the recruitment of cases

Table 1: Clinical types of dermatophytic infection at baseline

Clinical type	Baseline (*n*=157)	Percentage
T. corporis	14	9.1
T. cruris	21	13.3
T. faciei	5	3.1
More than one clinical type	117	74.5

3 times (range 1–9 times). [Table 2] Median duration of prior oral antifungal intake by the patients was 8 weeks (range 2–21 weeks), of which 115 (73.19%) had used oral itraconazole and 12 (8.0%) had used terbinafine, while 134 (89.93%) patients had already received more than 4 weeks of oral antifungal therapy at baseline.

Most common risk factors noted in the enrolled patients were topical steroid/mixed cream use, 125 (79.61%), and disease in family, 103 (65.11%). [Table 3] One hundred and twenty-seven (80.89%) patients had more than one risk factors [i.e. two risk factors in 66 (42.03%), and three risk factors in 18 (11.46%)]. The median duration of topical steroid use was 6 weeks (range 0–30 weeks). [Table 2] Other features observed in study patients at baseline and recurrent lesions at the end of 2 week are enlisted in Table 4, which included polycyclic border, eczematous changes, smaller annular plaques over the postinflammatory hyperpigmentation of previous lesions of tinea, etc., [Table 4] [Figures 1-4] The most commonly isolated fungal species at baseline and in the recurrent lesions was Trichophyton mentagrophyte.

One hundred and fifty-seven patients received oral itraconazole 100 mg once daily for 2 weeks. Eight (5.09%) patients were excluded from assessment (six patients deviated from the treatment protocol and two patients did not return for follow-up). Total 149 (94.90%) patients were assessed at the end of 2 weeks. At the end of therapy, only eight (5.36%) patients had clinical cure. One hundred and forty-one (94.63%) patients had recurrence. Recurrent lesions were due to partial response to therapy in 60 (42.55%) patients, recurrence after a short period of clinical improvement while on therapy in 63 (44.68%) patients, and symptoms aggravated in 18 (12.76%) patients. Mycological profile of the recurrent lesions at the treated site of dermatophytosis revealed that in 47 (33.33%)

Table 2: Characteristics of dermatophytosis enrolled in the study

Variables	Median	Range
Duration of disease (months)	3	1–12
Duration of topical steroid use (weeks)	6	0–30
Duration of use of oral antifungal (weeks)	8	3–21
Duration of symptom-free period prior to last recurrence (days)	6	0–32
Number of recurrence (times)	3	1–9
Lost for assessment (dropped out)	*n*=8 (Topical steroid use two, mixed cream use four, and two patient did not come for follow-up).	

Table 3: Risk factors of dermatophytosis enrolled in the study

Risk factors	Baseline *n*=157(%)
Topical steroid/Mixed cream use	125 (79.61%)
Disease in family members	103 (65.6%)
Associated atopy/eczema	98 (62.40%)
Pet at home	52 (33.12%)
More than one risk factor	127 (80.89%)

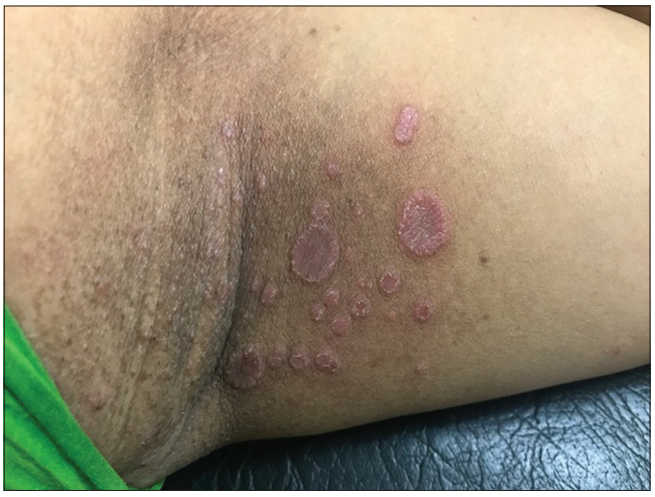


Figure 1: Recurrent lesions at the treated tinea site evolved into annular plaque at axilla

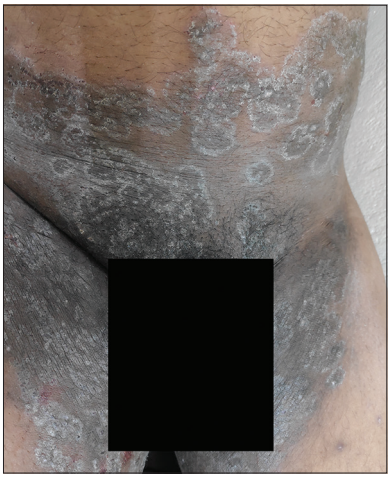


Figure 2: Increased predilection of tinea lesions at the waist and groin area

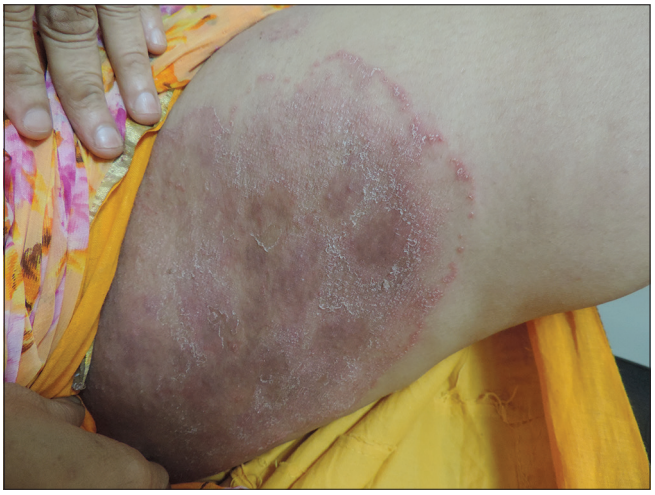


Figure 3: Recurrent papule and erythema at the treated tinea site subsiding with scale

Table 4: Morphological feature and evolution of dermatophytosis patients enrolled in the study and recurred after 2 weeks of itraconazole therapy

Variables		Baseline (*n*=157)	Patients with recurrence (*n*=141)
Border		109 (69.42%)	19 (13.47%)
Clear center		22 (14.01%)	8 (5.67%)
Change at border	Recurrent lesion at the treated site of fungal infection with no border	48 (30.57%)	110 (78.01%)
	Fungal lesion with polycyclic border	14 (8.91%)	-
	Fungal infection with pseudo-imbricate-like morphology	3 (1.91%)	-
	Recurrent lesion at the treated tinea site developed an incomplete border	58 (36.94%)	4 (2.83%)
Lesions at center	Dermatitic change at the treated site of fungal infection.	135 (85.98%)	121 (85.81%)
	Recurred lesions at the treated site of fungal infection evolved into annular plaques with clear center	7 (4.45%)	-
	Erosion at the treated site of fungal infection	6 (3.82%)	13 (9.21%)
	Pustule at the treated site of fungal infection	1 (0.63%)	-
	Recurred erythema at the treated site of fungal infection subsiding with scale	142 (90.44%)	76 (53.90%)
Recurrence of lesion on treated site		153 (97.45%)	141 (100%)
New site fungal infection		13 (8.28%)	-
Predilection of fungal infection for the frictional site		11 (7.0%) (Waist 5, inframammary 2, underneath ring 1, and sacred thread 3)	-
Clinical cure of fungal infection at few sites		13 (8.28%)	14 (100%)
Lesion increasing in size during the therapy		17 (10.82%)	-
Aggravation during the therapy		47 (29.93%)	17 (12.05%)
Violent aggravation of the existing lesion		25 (15.92%)	1 (0.70%)
Partial response to therapy		79 (50.31%)	74 (52.48%)
Recurrence after a short period of clinical cure		49 (31.21%)	33 (23.40%)

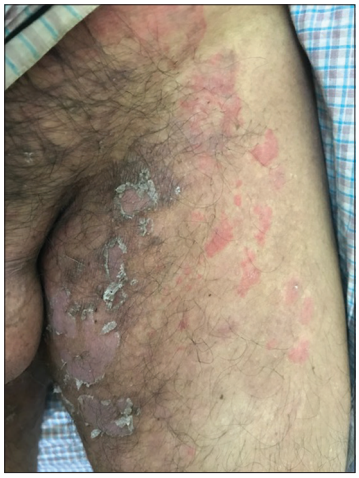


Figure 4: Recurrent erythema at the treated tinea site subsiding with scale

patients fungal elements were isolated and 94 (66.66%) patients did not show any fungal elements. [Table 5] Morphological analysis of the recurrent lesions after 2 weeks itraconazole revealed that 110 (78.01%) patients did not have clinical morphology of tinea infection as the initial erythematous border of tinea lesions recorded at baseline disappeared in them. [Table 4].

Discussion

In the present study, the average age of patients enrolled for the study was 32.26 years (range 12–61 years). A near similar age range was reported by others in various recent studies from India.[2,5]

Risk factors like topical steroid use, atopic dermatitis, disease in family, and contact with pets are known to complicate and prolong the course of dermatophytosis, alter the clinical morphology of tinea lesions, and develop dermatoses unrelated to fungal infection.[8-12,16,17,24] In the present study, risk factors observed were topical steroid use, disease in family members, atopic dermatitis, and contact with pets. In the patients with recurrent lesions, 66.66% were fungal test negative (developed dermatoses unrelated to fungal infection) and 33.33% had a fungal infection. Hence, it is likely that risk factors in the present study might have complicated the fungal infection and/or developed dermatoses unrelated to fungal infection.[8,9,10,11,16,17]

Recently few researchers reported the lack of correlation of clinical cure to antifungal susceptibility test. Similarly, there was no correlation between the recurrent lesions at the treated site of fungal infection to fungal test (i.e., treated tinea site developed adverse effects to prolonged topical steroid use, i.e., "topical steroid withdrawal syndrome"[16] and in atopic dermatitis patients with tinea infection evoked development of post-traumatic eczema/chronic eczema).[17] Also, risk factors like nail infection and disease in the family did not correlate with chronic fungal infection.[20-22] In the present study of dermatophytosis, a) clinical cure (5.36%) did not correlate with morphological cure (i.e., patients who lost initial fungal

Table 5: Clinical cure, mycological cure, recurrent lesion and mycological profile of recurred lesion following 2 weeks of itraconazole therapy

Assessed at the end of 2 weeks antifungal therapy. (*n*=149)		Assessment of recurrent lesion at the end of 2 weeks. (*n*=141)		
Clinal cure	Mycological cure	Clinical (*n*)	Mycological analysis	
			Fungal positive	Fungal negative
8 (5.36%)	102 (69.38%)	141 (94.63%)	47 (33.33%)	94 (66.66%)

border after therapy) (78.01%) and b) all recurred 141 (94.63%) patients did not have the fungal infection (i.e., 47 (33.33%) patients had fungal infection (test positive for fungus) and 94 (66.66%) patients had dermatoses unrelated to fungal infection (test negative for fungus)). Hence, it further supports the hypothesis that recurrent lesions at the treated site of dermatophytosis may have resulted from more than one risk factors complicated tinea, altered course, and morphology of the fungal infection, and/or development of dermatoses unrelated to fungal infection at the treated site of tinea like topical steroid withdrawal syndrome and post-traumatic eczema.[6,8,9,11,12,16,17,19,24,25]

Most of the recent studies from India have reported a rising trend of Trichophyton mentagrophyte (T. mentagrophyte) species in fungal infected.[4-6,26] Few researchers arbitrarily attributed it to migration, infection by virulent species, and transmission of infection to close contacts.[26-28] In the present study, the commonest fungal isolate was T. mentagrophyte at baseline and in recurrent lesion. Patients were not assessed for migration. However, authors hypothesized the high prevalence of T. mentagrophyte species in the study may have occurred due to chronic disease in the index case and resultant transmitted infection to close contacts, not vice versa, as very few patients developed infection at the new sites (i.e. previously uninvolved site). [Table 4]

Diagnosis of fungal infection on the skin is mostly clinical (characterized by an annular plaque, relative clear center, peripheral spread with continuous thin trailing scaly border).[29] However, there is a lack of consensus on the characteristic morphology of recurrent dermatophytosis. Hence, it often posed a diagnostic challenge in differentiating fungal infection from dermatoses unrelated to fungal infection. In the present study, we observed a wide range of changes like frequent recurrences, lesions recurred with diverse morphology, lesions recurred after varying intervals of symptom-free period and responded variably to antifungal therapy in enrolled, and patients who recurred after 2 weeks of itraconazole therapy in the study. [Tables 2 and 4] Few patients gave an interesting story of recurrent lesions (macule and papule) evolved into annular plaques over 1–2 weeks, [Figure 1] and examination revealed few patients had a predilection for fungal infection for the frictional sites.[Figure 2] Near similar increased predilection of fungal infection for the frictional sites was reported by others.[17] However, they did elaborate cause for such increased predilection of lesion for the frictional site. From the present study, authors hypothesized that the lesions that evolved into annular plaques on recurrence may be the fungal infection that had invaded the deep dermis following local immunosuppression induced by topical steroid use, and these acquired a classical morphology on its recurrence to the skin surface.[29] Second, the predilection of fungal infection for the frictional site may be due to skin barrier defect in atopic patients was aggravated by friction caused by tight cloth, which facilitated the binding of fungal arthroconidia to keratinized tissue and resulted in increased fungal infection at the frictional site.[30]

Limitation

Fungal isolates from the recurrent lesions were not tested for antifungal susceptibility.

Conclusion

This is the first study that identified the lesions that recurred at the treated site of dermatophytosis were fungal infection and dermatosis unrelated to fungal infection. Development of fungal infection and dermatosis unrelated to fungal infection in the presents study may be due to more than one risk factors altered/complicated the fungal infection and/or different properties of risk factor like: a) anti-inflammatory and immunosuppressive properties of topical steroid altered fungal infection, b) shift in immunity of Atopic dermatitis prolonged disease course of fungus, c) prolonged topical steroid use developed unique adverse effect "topical steroid withdrawal syndrome", d) Cutaneous trauma by fungal infection on Atopic dermatitis skin developed post traumatic eczema, e) disease in family members re-infected the treated tinea site, f) inadequate antifungal therapy, g) inherent skin barrier defect of Atopic dermatitis facilitated adhesion of fungus to keratinized tissue and/or h) fungal infection developed drug resistance. Hence, diagnosis of recurred lesion in the adequately treated dermatophytosis must be individualized and should be based on 1) duration of antifungal therapy received, 2) associated risk factors, 3) response to antifungal therapy, 4) evolution of recurrent lesion, and/or 5) fungal test.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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