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ORIGINAL ARTICLE

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Study the effect itraconazole and luliconazole in dermatophytosis patients with associated atopic dermatitis: A prospective observational

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ABSTRACT

Background: Few researchers believed that the association of atopic dermatitis may alter the treatment outcome in dermatophytosis patients due to the shift in immunity to ward Th2 cytokines. However, there is a paucity of studies that analyzed the clinical and mycological cure rate at the end of 4 weeks of antifungal therapy (itraconazole and luliconazole cream) in dermatophytosis with associated atopic dermatitis.

Method: A total of 246 patients of dermatophytosis with associated atopic dermatitis and positive mycological tests (KOH and/or fungal culture) were enrolled to receive oral itraconazole 100mg twice daily and luliconazole 1% cream once daily application for 4 weeks. Patients were assessed for clinical cure at the end of therapy. Patients who did not achieve clinical cure were subjected to mycological tests (KOH& fungal culture) for identifying fungal infection.

Results: Eighteen (n=18) patients dropped out. At the end of the study, 228 patients were analyzed clinically. 43 (18.85%) patients achieved clinical cure. 185 (81.1%) patients who did not achieve clinical cure were subjected to fungal test therapy (KOH and fungal culture), of which 23 (12.43%) patients were positive for the fungus. Atopic dermatitis and diabetes were the frequently observed risk factors.

Drawback: An anti-fungal susceptibility test was not done.

Conclusions: In the present study, the proportion of patients showing clinical cure was low in dermatophytosis with associated atopic dermatitis. The patients who did not achieve clinical cure were composed of fungal positive in mycological tests, and there were around one to seven cases. The present study's low clinical cure ratewas possibly associated with atopic dermatitis, complicated fungal infection (prolonged disease course), and development of dermatosis unrelated to fungus (post-traumatic eczema).

KEYWORDS

Dermatophytosis; Tinea; Atopic dermatitis; Clinical cure; No cure; Dermatosis unrelated fungus; Treatment outcome

ARTICLE HISTORY

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Introduction

The treatment failure in dermatophytosis is attributed to more than one risk factor complicating the course of fungal infection and/or evoking the development of various other dermatoses (such as topical steroid withdrawal syndrome, eczematous changes, allergic contact dermatitis, and adverse effects to topic drugs used) at the site of fungal infection [1-15]. Few researchers believed skin barrier defect of atopic dermatophytosis contributed to the development of widespread infection by facilitating the adhesion of fungal arthroconidia keratinized tissue, shifting immunity towards Th2 cytokines and cutaneous trauma induced by fungal infection evoking development of post-traumatic eczema [4,14,16,17]. Hence, it's expected that the association of atopic dermatitis will alter the clinical cure and development of dermatosis unrelated to the fungus at the site of dermatophytosis. However, there is a paucity of studies analyzing the treatment outcome of dermatophytosis associated with atopic dermatitis [4].

The present study analyzed the proportion of clinical curein study patients and fungal-positive cases using mycological tests (KOH wet-mount and fungal culture) in treatment failure /no-cure dermatophytosis with associatedatopic dermatitis following 4 weeks of oral itraconazole therapy and luliconazole cream.

Inclusion criteria

Patients of dermatophytosis with associated atopic dermatitis, not on oral antifungal treatment in the last month, not on topical steroids for the last 3 months at baseline, age greater than or equal to years, and both genders were enrolled in the study.

Exclusion criteria

Patients with doubtful dermatophytosisor bacterial infection at the same site were excluded. Pregnant and lactating females and patients with immunosuppression, immunosuppressive therapy, or associated fungal infection of the nail or hair were also excluded.

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Design

A prospective observational study was initiated after obtaining the institutional ethical committee approval (IEC/ AIIMS BBSR/ PG Thesis/2022-23/66) and written informed consent from patients.

Sample size

A sample size of 246 patients was calculated considering the confidence interval of 95%, a prevalence rate of 20% dermatophytosis in the adult population, with a margin of error of 5% [18].

Statistics

Variables were assessed using IBM software version 22. Categorical data were expressed as frequency and percentage, and continuous and discrete data were expressed as mean and median.

Materials and Methods

The study was conducted between June 2022 and 2023 at the tertiary care hospital of Odisha, India. A total of 246 consecutive dermatophytosis patients with associated atopic dermatitis who satisfied inclusion and exclusion criteria were enrolled. The demographic details of the patients, duration of disease, details of the antifungal drugs used, and risk factors were collected using a pre-designed proforma.

Intervention

As the treatment regimen for dermatophytosis associated with atopic dermatitis tinea is unknown, all enrolled patients were administered 100 mg of oral itraconazole twice a day along with luliconazole 1% cream once daily for 4 weeks as per the treatment proposed by Rengasamy et al., [19]. The patients were allowed to use oral levocetirizine 5 mg on an as-needed basis (max 20mg/day) for the itch.

Definition

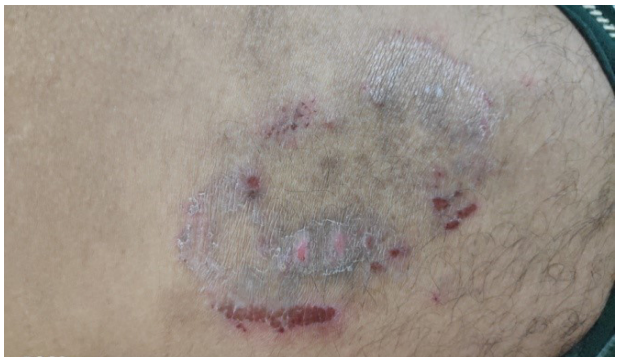
Clinical cure was considered when the clinical symptoms and signs improved with or without post-inflammatory pigmentation. All other cases with partial/brief periods of improvement or those experiencing aggravation in clinical signs and symptoms were considered cases of treatment failure/ no cure.

Assessment

Patients were assessed for clinical care and treatment failure/ no cure. Patients who did not have a complete clinical cure (treatment failure/ no cure) were further assessed for mycological evidence of fungal infection using KOH wet-mountand fungal culture.

Results

A total of 246 dermatophytosis patients with associated atopic dermatitis were enrolled in the study [Figure 1a and b, 2a and b, and Figure 3]. Age ranged from 18-55 years (mean age 36.34 ±8.27 years), male to female ratio was 138:108 (1.2:1). Most patients enrolled in the study were of clinical types steroid modified and chronic tinea [Table 1]. The associated risk factors of the enrolled participants are shown in Table 2. Oral antifungal therapy received by study patients before enrolment is shown in Table 3. *Trichophytonmentagrophyte* was the commonest fungal species isolated from patients at baseline (67%).



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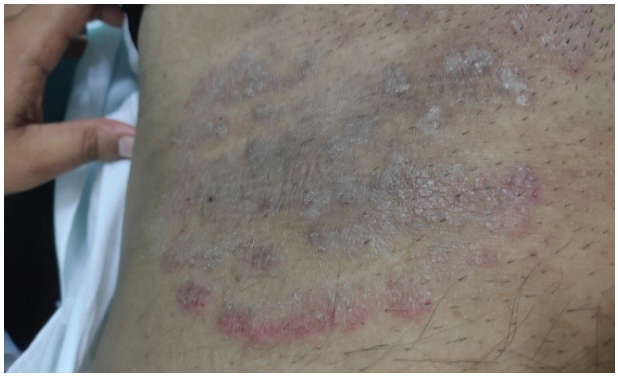
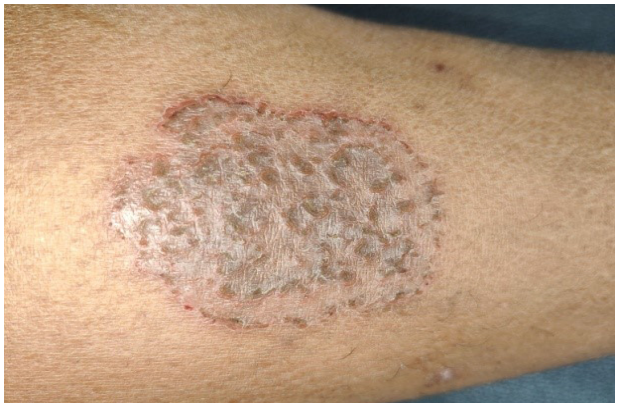


(b)

Figure 1 (a and b). Tinea presenting as excoriation and lichenified change over the healed site of fungal infection at the shoulder and abdomen.



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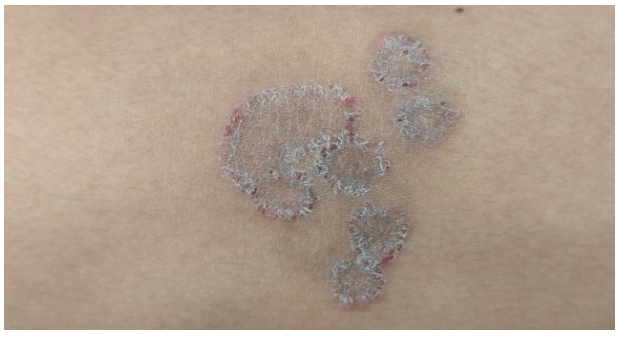

(b)

Figure 2 (a and b). Tinea on leg and abdomen area presenting as a circular plaque with lesion having excoriation and scale/ crust over post inflammatory hypopigmentation of tinea.

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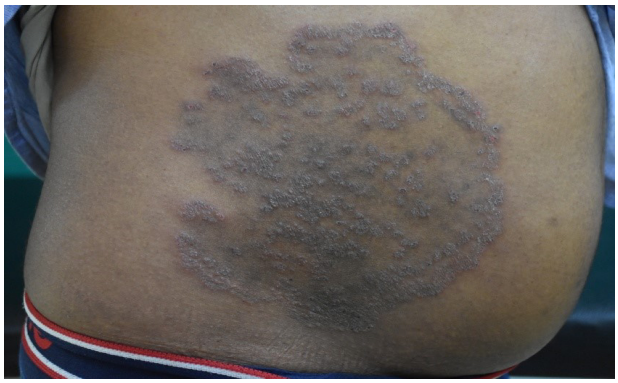

Figure 3. Tinea on the abdomen presenting as a papule subsiding with scale over the post inflammatory hyper pigmentation of tinea.

Table 1. Clinical types of dermatophytosis enrolled at baseline as per INTACT criteria [19].

Sl no	Clinial Types	Number (%)
1	Treatment naive	6(2.43)
2	Steroid modified tinea	67(27.23)
3	Resistance tinea	5(2.03)
4	Recurrent tinea	23(9.34)
5	Recalcitrant tinea	42(17.07)
6	Tinea incognito	43(17.47)
7	Chronic tinea	60(24.39)
Total		246(100%)
Extensive disease		11(4.47)

Table 2. Risk factors in enrolled dermatophytosis patients with associated atopic dermatitis.

Sl no	Risk factors	Number of patients (N=246)
1	Atopic dermatitis	246(100%)
2	Diabetes	118(47.96%)
3	Disease in family	13(5.28%)
4	Both Atopic dermatitis and diabetes application	142(57.72%)

Table 3. Oral antifungal treatment received prior to enrolment.

Sl no	Duration of oral antifungal use	Cases (%)	Median period of oral drug use (Weeks)
1	>3 month	115(46.74%)	18 (range 13-37)
2	1-3months	82(33.33%)	6 (range 4-12)
3	<1month	43(17.47%)	2 (range 1-3)
4	No treatment	6(2.43%)	-

Eighteen (7.31%) patients dropped out. Of the 228 patients assessed clinically, only 43 (18.85%) patients achieved clinical cure. In the mycological assessment of patients who did not achieve a complete clinical cure, fungal test-positive cases were present in 23 (12. 43%) patients [Table 4].

Table 4. Showing patients enrolled, drop out, patients assessed for clinically and partial cure assessed using mycologically for fungal positive and negative cases at the end of 4 weeks oral itraconazole therapy.

Enrolled	Dropped out	Assessed clinically at 4weeks (N= 228)		Mycological assessment of partial cure/no cure/ treatment failure (N= 185)			
		Clinical cure	No cure/ treatment failure	Fungal positive			Fungal test negative
(N=246)	(N=18)	43(18.85%)	N=185(81.1%)	23(12.43%)			162(87.56%)
				Culture & KOH positive	KOH positive	Culture positive	
				8	11	4	

Discussion

In the present study, the proportion of patients achieving clinical cure at the end of antifungal therapy was low (18.85%), which is similar to the previous study by Sirka et al. low clinical cure following 2 weeks of oral itraconazole and topical luliconazole therapy [2]. Contradictory to the study by Majid et al. who achieved a pronged clinical mycological cure in dermatophytosis patients following 2 weeks of 250 mg/day oral terbinafine therapy [5].

The cause of partial cure (treatment failure/ relapse/ no cure) in adequately treated patients of dermatophytosis is not clear. Majid et al. concluded relapse in patients of dermatophytosis in their study was due to inadequate therapy [5]. Other authors have attributed the recurred lesion in dermatophytosis patients either to the emergence of resistance to conventional antifungal agents or due to the occurrence of various other types of changes at the site of dermatophytosis development of various dermatoses unrelated to fungal infection (adverse effect unique to prolonged topical steroid use "topical steroid withdrawal syndrome" and cutaneous trauma at the site of tinea infection on atopic skin inducing development of post-traumatic eczema), allergic contact dermatitis to topical antifungal cream or due to development of Wolf's isotopic response [2-5,7-10,13,15].

In the present study, the proportion of patients who did not achieve a complete clinical cure following antifungal therapy was as high as 81.1%. Mycological tests did not demonstrate fungal elements in 87.56% of no-cure cases who experienced only partial/no improvement at the end of therapy. A similar higher proportion of partial/no cure was reported by other authors among patients of dermatophytosis in recent years [1,2,20]. Sirka et al. in their previous study of dermatophytosis,

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reported that recurred patients were composed of fungal positive and negative patients on mycological tests at the end of antifungal therapy. They hypothesized that developing fungal negative and positive lesions at treated tinea may cause a low clinical cure [2]. The discordance in the rates of clinical and mycological cure among patients of dermatophytosis might have been due to either lower sensitivity of the various mycological tests used for the demonstration of fungal elements [21] or due to the emergence of various other dermatoses at the site of tinea infection [4,10-13].

As a large proportion of such patients also had associated atopy, a prolonged itch-scratch cycle at the site of chronic dermatophytic infection might have induced the emergence of changes due to atopy and developed acute or chronic eczema at the sites of tinea infection [2].

Prolonged self-use of topical steroid creams, which are available over-the-counter, can lead to adverse effects similar to the condition like topical steroid-damaged facies, which can result in patchy to diffuse erythema, telangiectasia, scaling, dryness, and increased sensitivity and irritation of the affected skin. Changes unique to prolonged topical steroid use have adverse effects on topical steroid withdrawal syndrome, which may present with diverse morphology, episodes of erythema, and burning pain, and episodes may continue to appear for many months after the topical steroid use. The eczematous change at the dermatophytosis site in persons with atopy or adverse effects similar to topical steroid-damaged facies due to prolonged use of topical steroids may be mistaken for the recurrence of dermatophytic infection. Topical antifungals may induce eczema change due to allergic contact dermatitis at the application site. Also, in most instances, one or more of these conditions may coexist, resulting in confusion [15,4,10]. In addition, the emergence of resistance might play some role in complicating the situation. Further studies are necessary to elaborate on the exact clinical patterns and evolution of these coexistent changes among patients of recurrent dermatophytosis.

Various previous publications have implicated several other risk factors for recurrence and prolonged course of dermatophytosis. These include infection among family members or close contacts, transfer of infection from infected pets, changes in clothing patterns, and the emergence of newer species of dermatophytosis due to migration of population [1-10,14,22,23]. However, in a study by Tuknayat et al. there was no direct correlation between chronicity of dermatophytic infection and presence of disease among family members [24]. A study by Kalekhan et al. did not find a rise in the tinea unguium in a recurrent dermatophytosis study [25].

There is a rising trend of risk factors like topical steroid use, atopic dermatitis, and patients having more than one risk factor in dermatophytosis [1-3,22]. Risk factors like topical steroid use and atopic dermatitis are attributed to the development of a wide range of changes in fungus and fungal-infected sites by their unique properties [4,6-10,14,23]. In the present study, the frequently observed risk factors were prior history of use of associated atopic dermatitis and diabetes [Table 2]. Hence, such changes may be explained as atopic dermatitis complicating the fungus and/or evoking the development of lesions like post-traumatic eczema in such patients. In the present study, drug resistance was not studied.

Conclusions

In the present study, the proportion of patients showing clinical cure was low in dermatophytosis with associated atopic dermatitis. The patients who did not achieve clinical cure were composed of fungal positive in mycological tests, and there were around one to seven cases. The present study's low rate of clinical cure was possibly associated with atopic dermatitis, complicated fungal infection (prolonged the course of disease), and development of dermatosis unrelated to fungus (post-traumatic eczema).

Drawback/Limitations

Drug resistance testing was not done in the present study.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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