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TCA as an effective augmentation therapy in case of resistant and recurrent tinea cruris & corporis

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ABSTRACT

Background: The widespread resistance and recurrent cases of dermatophytosis have become a real challenge.

Aim and Objectives: To study the efficacy of augmented therapy against recurrent dermatophytosis by trichloroacetic acid peeling added to systemic itraconazole.

Method: 13 Egyptian patients (7 males and 6 females) having dermatophytosis were enrolled in the study. Trichloroacetic acid 30% was applied over the lesions weekly for 5 successive weeks with systemic itraconazole 400 mg daily for 2 weeks and then 100 mg daily for one month; thereafter, patients were followed up every 2 weeks for 6 weeks.

Results: Of the 13 patients, 2 patients didn't complete the study; of the remaining 11 patients, 72% of patients (8 patients) were cured 2 weeks after the last application, while of the remaining 3, 2 had recurrence after initial response (18%), and 1 patient was considered resistant by showing minimal response (9%).

These findings indicate that 5 weeks ' treatment with topical TCA 30% application is a good augmentation treatment with systemic itraconazole in resistant and recurrent dermatophyte infection.

Limitations: A relatively small sample size and lack of fungal strain identification are the shortcomings of this study.

Conclusion: Trichloroacetic acid peel is a cheap, available, and useful option as an adjuvant in the treatment of resistant & recurrent dermatophytic infection.

KEYWORDS: *Dermatophytosis, recurrent tinea, trichloroacetic acid peel, topical treatment.*

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1. INTRODUCTION

Tinea, another name for dermatophyte infections, is still a major global public health issue. More than 40 species of common and uncommon contagious filamentous fungi are known as dermatophytes, and they can infiltrate keratinized tissues to cause superficial infections of the skin, nails, and hair [1].

Contact with infected people, animals, soil, or contaminated fomites can result in infection. It is possible for secondary spread from other infected body sites. Dermatophyte infections are thought to be the most prevalent fungal illnesses in people [2].

Researchers estimate that cutaneous fungal infections like tinea cruris and tinea corporis affect 20–25% of people worldwide [3]. Due to high temperatures and elevated humidity, dermatophyte infections are more common in developing

and tropical nations [4].

Over 51 million doctor visits and an estimated 29.4 million cases of superficial fungal infections have been reported in the United States [5]. Tinea cruris is more common in male adolescents and adults, with the majority of patients being male [6]. The rise in dermatophytosis cases and the identification of resistant infections have raised global concern [7].

The skin problems caused by tinea corporis and tinea capitis, along with onychomycosis and tinea pedis, are all different forms of dermatophytosis. [8] The most common skin fungi that like to live on humans are Microsporum (M) audouinii, Trichophyton (T) rubrum, interdigitale, T. tonsurans, violaceum, and T. soudanense. These species typically produce desquamative and itchy lesions with minimal inflammation.

On the other hand, when they infect humans, zoophilic species—mostly T. mentagrophytes and M. canis—and geophilic species cause more inflammatory lesions [9]. In the past, immunocompromised patients, particularly those on corticosteroids, have been reported to exhibit extensive dermatophytosis that is restricted to the stratum corneum [10].

In 2018, Indian dermatologist warned about the worrying increase in resistant skin infections caused by the T. mentagrophytes species, likely due to the overuse of topical antifungals and corticosteroids. T. mentagrophytes is thought to be zoophilic and linked to cases of tinea corporis, whereas T. interdigitale is thought to be anthropophilic and causes tinea pedis [12]. Within the T. mentagrophytes species complex, the dermatophyte that caused the outbreak in India was assigned to a specific genotype (i.e., genotype VIII).

Its ability to spread from person to person without needing contact with infected animals led to a debate among scientists, which resulted in the recent naming of a new species, Trichophyton indotineae. The new name is clinically relevant and could raise awareness, even though it is taxonomically incorrect to separate T. indotineae from T. mentagrophytes as a new species [13]. A compatible sequence uploaded since 2008 was discovered while searching for genotype VIII sequences deposited in GenBank, indicating that it may have been subtly circulating for over a decade. Furthermore, the same study revealed the presence of the novel T. indotineae in both humans and animals in Southeast Asia and the Middle East [10]. Cases have been reported on every continent since the recent Indian outbreak spread around the world, with the Americas reporting the most recent cases [12]. Although the Indian subcontinent was epidemiologically associated with the first cases, more recent research has found cases that have no such association. Due to reporting bias, this raises questions regarding the pathogen's possible local circulation outside of the Indian subcontinent, including in nations that are not yet included on the epidemiological map [14].

2. METHODS

After providing their consent, patients with active tinea infections—tinea cruris and corporis—who were willing to take part in the study were added. After stopping the oral antifungals, all participants received systemic antifungals (fluconazole, terbinafine, and itraconazole) for at least four weeks, during which time they developed resistance and recurrence. Children under the age of eighteen and pregnant women were not included.

On the initial visit, microbial culture and scale scraping were performed. A complete blood count, liver enzymes, and a renal function test were performed as a baseline and again after three weeks. To create a 30% w/v TCA, 30 g of powdered trichloroacetic acid was mixed with 100 mL of acetone. During the first visit, a test was conducted for one site for two reasons. First comparing the outcomes of this site treated with both TCA and systemic antifungal to other sites treated with systemic antifungal alone as a split control, then the patient's tolerability to TCA will be tested.All lesions, including the active border, were covered with a piece of gauze that had been gently squeezed to make it wet but not dripping with TCA 30% solution. Notably, the active border is typically highlighted by TCA frosting. Ten milliliters (3 grams of trichloroacetic acid) of TCA could be used in a single treatment session.The scrotum was protected when TCA was applied in the inguinal region. If the scrotum was inadvertently touched, it was washed with saline (this only happened to one patient in his second session; no negative effects on the scrotal skin were observed a week later during the third session). In order to reduce the burning pain and the risk of ulceration, patients were instructed to apply a healing cream, such as Mebo®, twice daily following the session. This was especially recommended for obese patients because of the frequent friction or adhesion between the thighs' skin folds. For five weeks in a row, the treatment was repeated weekly (a three-day delay was deemed acceptable).

More sessions were required to make up for the patient's missed sessions, which resulted in recurrence (keep in mind that mild itching usually happens after peeling, but severe itching is typically an early sign of recurrence occurring even before erythema or active borders are seen clinically). During the study period, oral itraconazole 400 mg/day was administered to all patients for two weeks in a row, followed by 100 mg/day for one month.

3. RESULTS

A total of 13 Egyptian patients were recruited in this study. Two patients left the study due to irregular adherence to the study protocol. In all, 11 patients (6 males and 5 females) were included for analysis. Table 1 displays the data on treated patients and their treatment outcomes. All patients had inguinal involvement (T. cruris); there were 3 patients who had trunk and lower limb affections, and 4 patients who had upper limb involvement besides inguinal and lower limb affection. After 21 days at room temperature, the culture tested negative when incubated at 37°C on fungal media (Sabouraud Dextrose Agar—SDA), but it was positive for Trichophyton species (T mentagrophytes and rubrum) in 4 patients, which is about 36% of those in the study. Although the diagnosis of the treatment-resistant case was confirmed through skin biopsy, histopathological analysis, and the flaring clinical presentation of the infection in all cases, cultures were negative for fungal growth in most instances. Eight patients (72% of the study participants) showed complete clearance without recurrence. Two patients (18% of the study participants) showed a recurrence after 3–4 weeks. There was only one patient who showed no response to treatment (9% of patients). These findings indicate that augmented treatment with itraconazole and topical TCA (30% peeling) is effective in eradicating resistant and recurrent tinea infections. All patients reported a burning sensation and itching on application of TCA on the inflamed areas. Patients reported decreased burning during subsequent sessions. No patients reported major systemic side effects due to TCA application.

Table 1 provides information about the treatment outcomes for patients.

Age/sex	Area	Duration	Prior treatment	outcome
41 years, male	B, I, LL, AB, UL	8m	I	CL
45 years, male	B, I, LL	4m	F	CL
36 years, male	B, I, AB	2m	T ,F	CL
47 years, male	B, I	5m	T ,F	Re 3w
26 years, male	B, I, LL, UL	3m	T	CL
33 years, male	B,I,C,AB	7m	I , T	CL
24 years, female	I, LL, AB, UL	4m	I ,F	CL
38 years, female	B, I	6m	F	CL
54 years, female	B,I,C,AB	9m	I ,F	Re 4w
45 years, female	B, I	8m	T,F	CL
62 years, female	B, I, C , LL, AB, UL	1 year	T,I ,F	Non responder

Area of involvement:
B: buttock, C: chest, F: face, I: inguinal, LL: lower limb, UL: upper limb, AB: abdominal
Prior treatment received: I:itraconazole, T : terbinafine, F: fluconazole.
Outcome: CL: clearance of lesions, Re: recurrence

Case presentation:

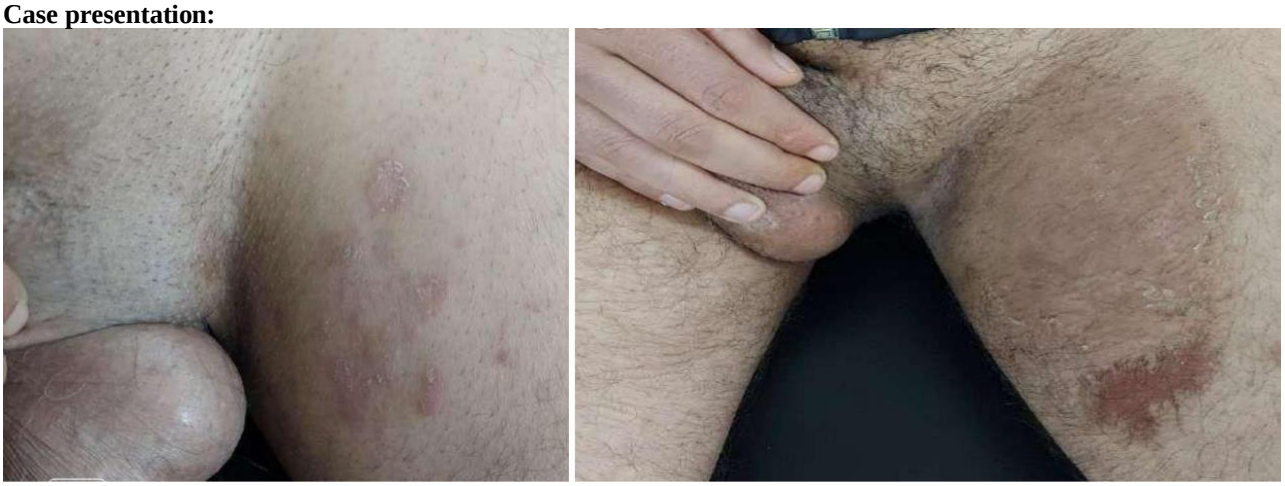

Fig. 1A 45 years old male patient with tinea cruris 6 m ago, left Before treatment, right after 2 weekly sessions.

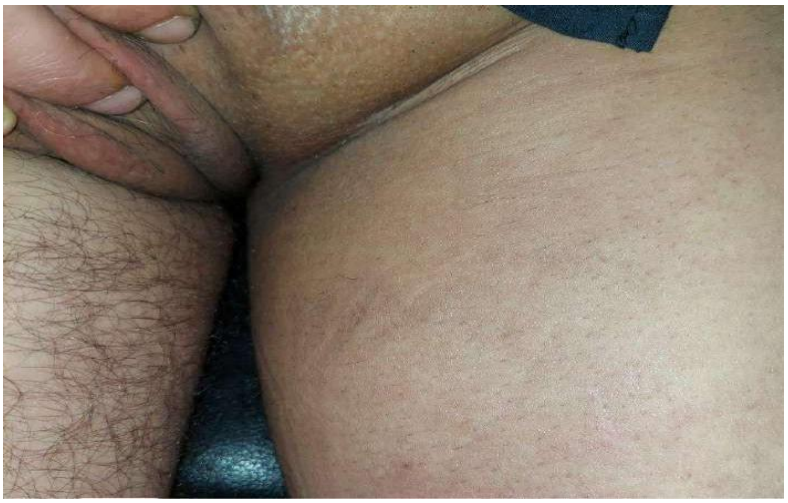

Fig. 1B patient showed complete cure after treatment with no itching reported.

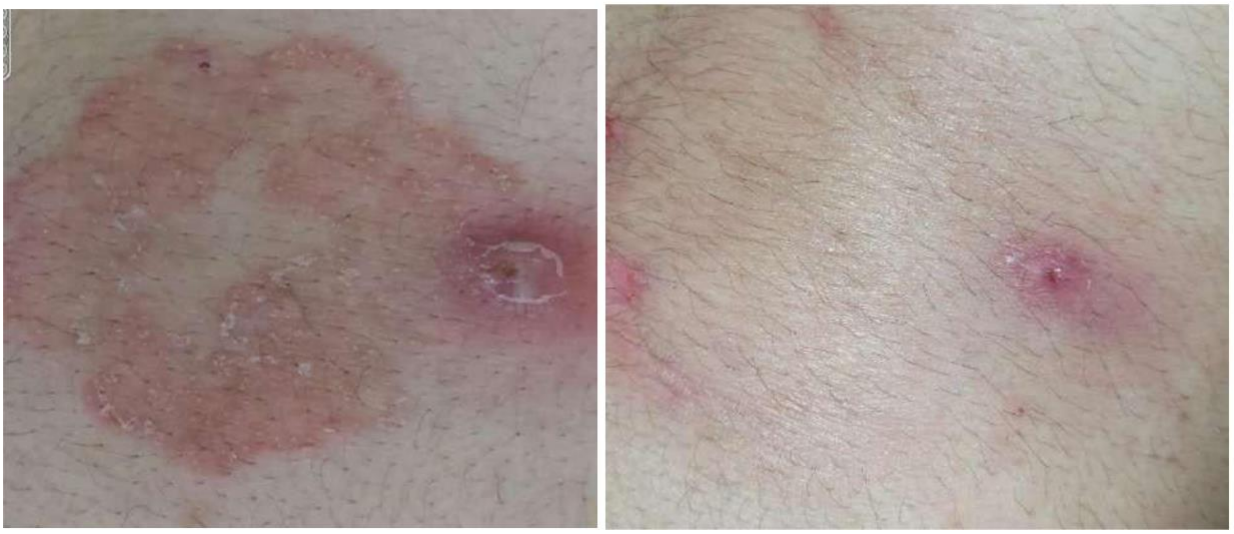

Fig. 2A 33 years old male patient with tinea cruris & corporis, in the left the chest is affected by tinea corporis (note presence of abscess due to intense itching & 2ry bacterial infection at the 3o clock of the left pretreatment), right after 1 week only (the 1st test session for this site only)

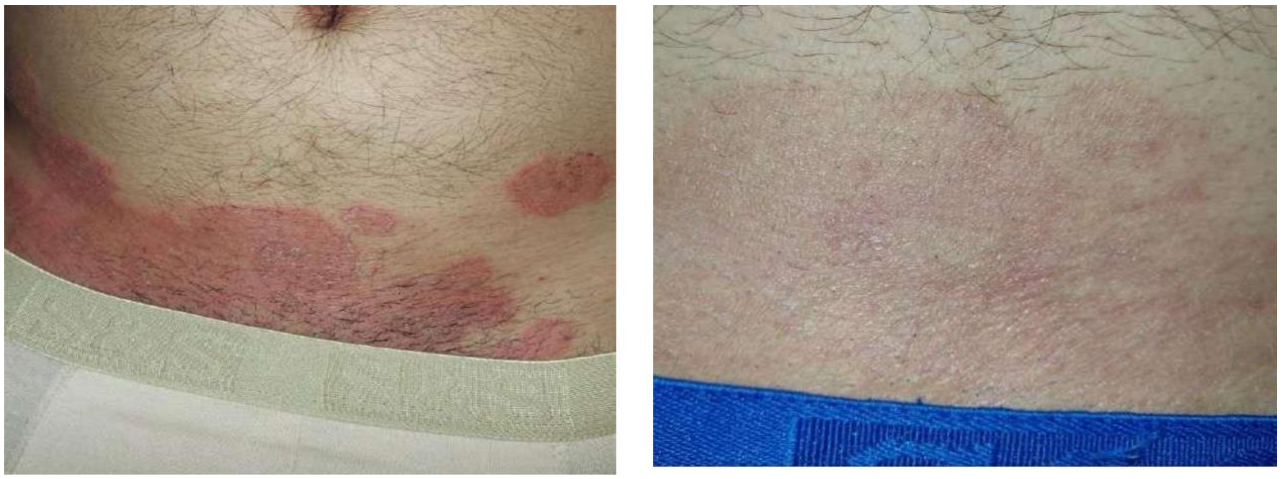

Fig. 2B same patient with tinea cruris & corporis, at pubic area, left Before treatment , right after 1 week oral antifungal only elucidating the effectiveness of combining TCA peeling to oral antifungal as more noticeable response is seen

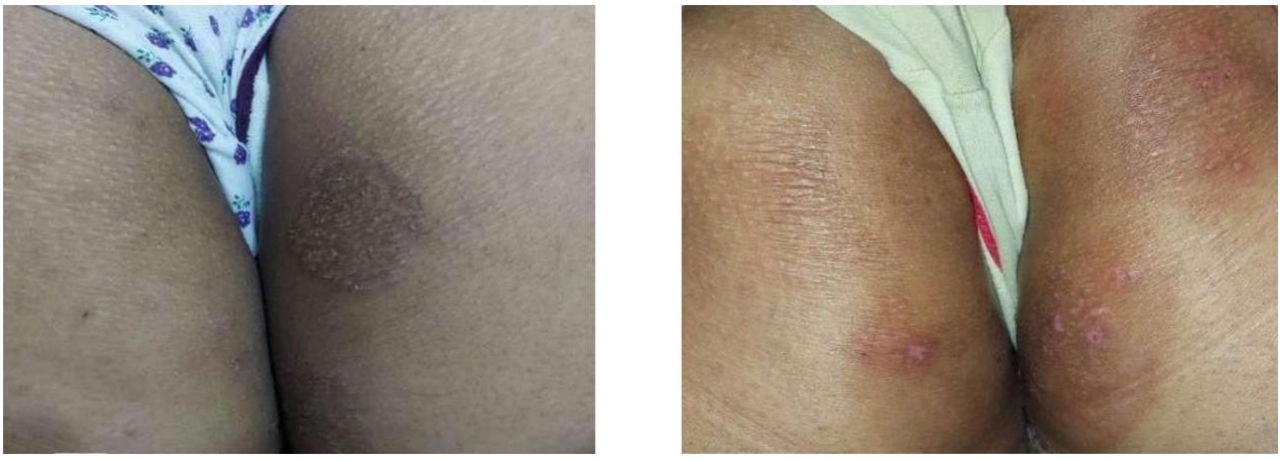

Fig. 3A 38 years old female patient with tinea cruris & corporis affecting the buttock, left Before treatment, right after 2 weekly sessions. (of note, her elder 2 sisters 45years old &54 years old were infected to

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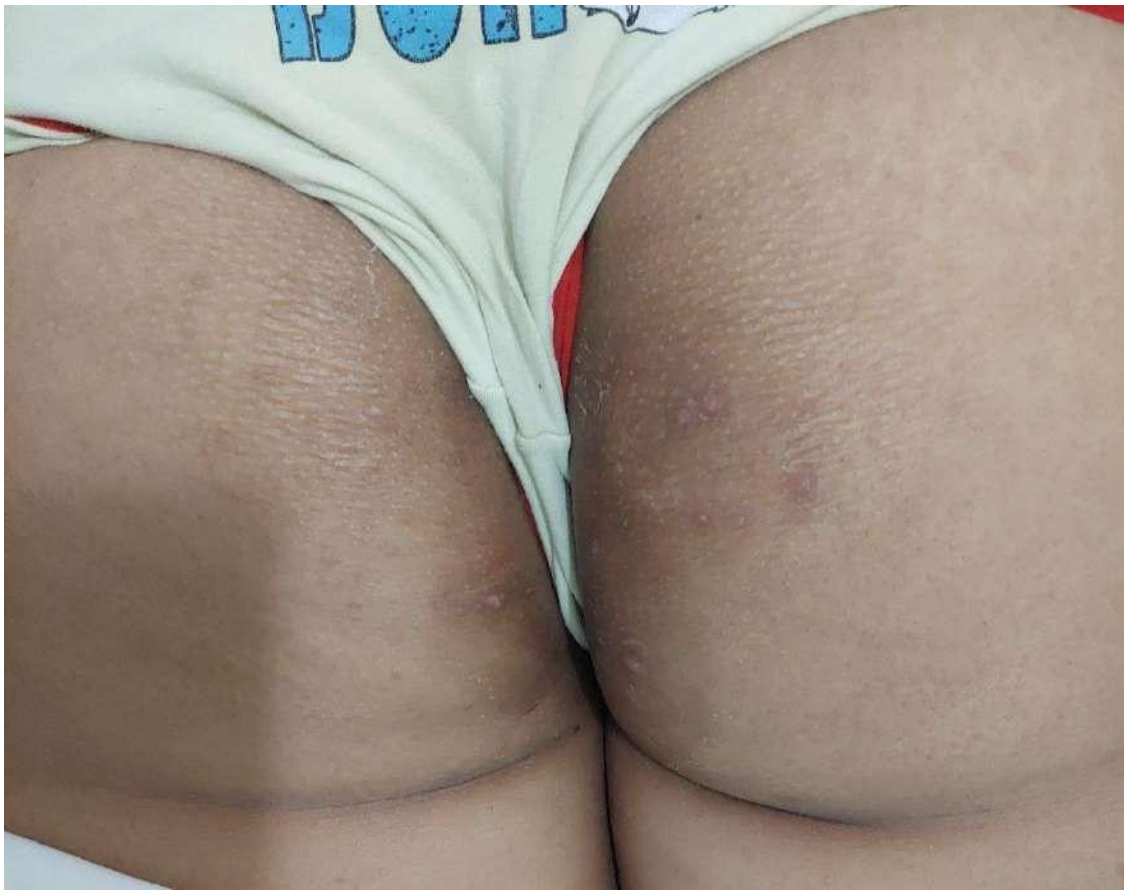

Fig. 3B showed marked improvement after treatment.

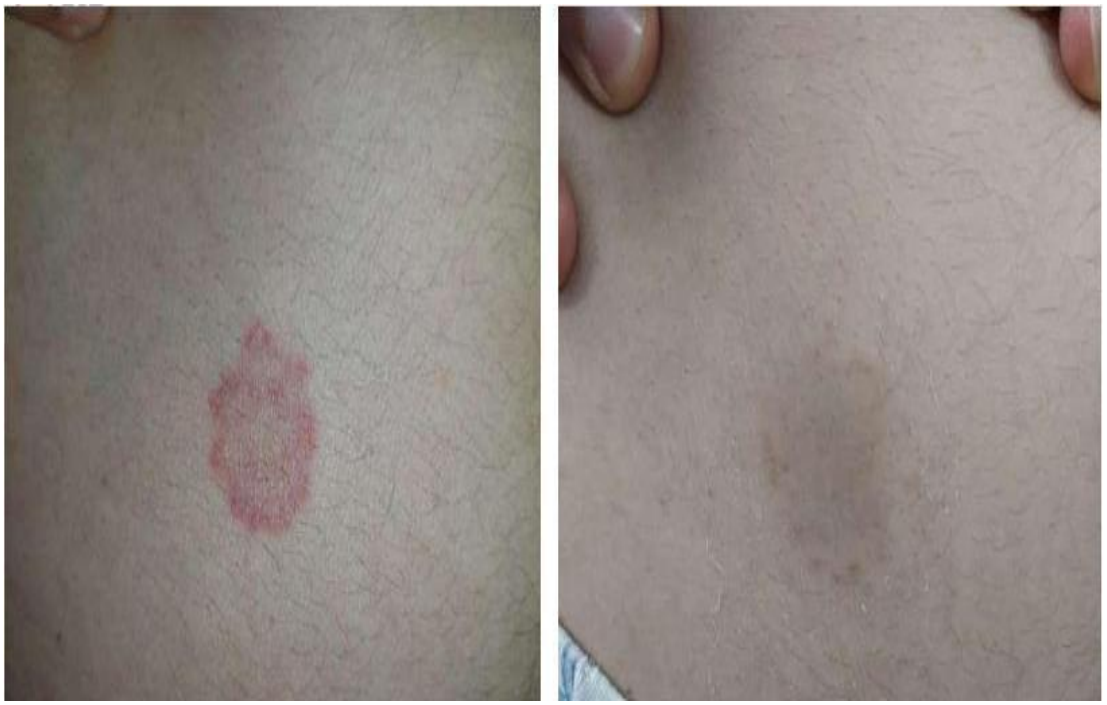

Fig. 4A 41 years old male patient with tinea cruris & corporis, left Before treatment, right after 2 successive sessions. (of note, his wife got infected too)

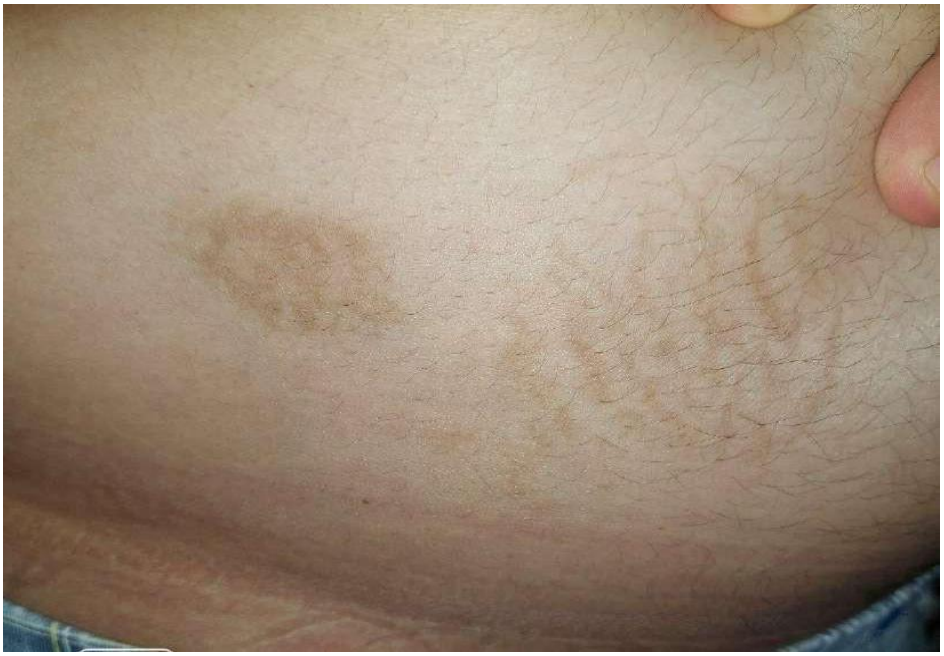

Fig. 4B showed marked improvement with only PIH remaining after treatment.

4. DISCUSSION

Dermatophyte resistance to terbinafine and azoles has garnered renewed attention as a result of the emergence and global spread of T. indotineae. Researchers reported the first instance of terbinafine-resistant dermatophytes in 2003 [15]. Of the 30 strains of T. rubrum taken from onychomycosis patients who didn't get better after six months of taking oral terbinafine, only one showed a higher minimum inhibitory concentration (MIC) to terbinafine and other squalene epoxidase inhibitors. Researchers later linked point mutations in the SQLE gene, which codes for squalene epoxidase and is involved in the biosynthesis of ergosterol, to terbinafine resistance [16].

These mutations, concentrated in hotspots, substitute key positions in the enzyme's amino acid sequence—393Leu, 397Phe, 415Phe, and 440His. T. rubrum, T. interdigitale, and T. indotineae all contain them. Phe397Leu and Leu393Phe are the substitutions that are most commonly reported. Unlike Phe397Ile, Phe415Ile, Phe415Val, and His440Tyr, they are linked to a marked rise in MICs to terbinafine.

Outside of India, the USA, Japan, and Europe provide information on dermatophyte terbinafine resistance. In the USA, the highest rates of terbinafine resistance have been found, with 4.3% of T. interdigitale samples and 3.6% of T. rubrum samples showing resistance [17]. Less frequently reported elevated MICs to azoles are of particular concern for isolates of T. indotineae. So far, two ways that T. indotineae can resist treatment have been found: one is by making more of the target protein due to having extra copies of CYP51, and the other is by pumping the drug out of the cell using more ABC-type transporters.

The assessment of dermatophyte sensitivity to antifungal agents needs more focus in light of these findings. Trichophyton species need regular testing to see how sensitive they are to antifungal drugs, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has changed a standard broth microdilution method for these fungi. Howspecies, such as T. rubrum, exhibit poor conidiation, which complicates the use of this method; additionally, even for species that conidiate well, such as those in the T. mentagrophytes complex, this method remainsomplex species, this method is still slow, requires a lot of work, and needs skilled workers. However, some species (like T. rubrum) have poor conidiation, making it hard to use, and even for species that conidiate well (like T. mentagrophytes complex species), this method is still time-consuming, labor-intensive, and requires skilled workers [18].

Gradient concentration stripes of terbinafine have been created and tested, but the outcomes have been disappointing. As an alternative, the strain's wild-type phenotype can be assessed using a medium containing terbinafine [19].

We need to work on turning in vitro MICs into useful clinical breakpoints for different dermatophyte species and create simpler, cheaper methods that regular labs can easily use to test how sensitive these fungi are to antifungal drugs. The French chemist Jean-Baptiste Dumas created trichloroacetic acid for the first time in 1839 [20]. Early in the 20th century, its application in dermatology—specifically, chemical peels—began to gain traction, and over time, concentrations of about 30% became the norm for medium-depth chemical peels. As contemporary dermatological techniques advanced in treating wrinkles, acne scarring, and melasma, the specific use of TCA 30% for skin treatments most likely appeared in the 1950s and 1960s. The TCA concentration affects the peeling depth [21].

Higher concentrations of TCA can be used safely without causing any systemic effects because it is a self-neutralizing chemical that is not absorbed into the bloodstream. TCA is occasionally applied to bleeding spots as a hemostatic or cautery agent [22]. It destroys collagen in the upper skin layers and causes proteins and skin cells to clump together and die. Over a few days, necrotic layers peel off, and adnexal collagen causes the skin to re-epithelize [23].

A pH of 3.0 or lower is fatal to fungi, so acidification can be used as a fungicidal tool. Although it required prolonged application, vinegar (5% acetic acid) was effective in treating tinea pedis [24]. Besides helping to remove as much fungus as possible while the dead skin is shedding, this can be seen as a way TCA peeling works in treating tinea.

In the current study, All patients had inguinal involvement (T. cruris); there were 3 patients who had trunk and lower limb affections, and 4 patients who had upper limb involvement besides inguinal and lower limb affection. After 21 days at room temperature, the culture tested negative when incubated at 37°C on fungal media (Sabouraud Dextrose Agar—SDA), but it was positive for Trichophyton species in 4 patients, which is 36% of those in the study.

In the current study there were Eight patients (72% of study participants) demonstrated full clearance without recurrence in the current investigation. After three to four weeks, two patients (18% of the study participants) experienced recurrence. Only one patient, a 62-year-old woman (9% of participants), was deemed resistant to this treatment protocol because she did not respond to treatment.

The findings of this study show that using itraconazole along with 30% TCA peeling sessions is effective for treating stubborn and returning tinea infections. We obtained similar results to support the current study, using a slightly different approach but maintaining the same mechanism of action. Since there are no new antifungal medications, Saoji and Madke

[25] showed that using 30% salicylic acid to peel off the top layer of skin is safe and might be a useful treatment for resistant tinea infections.

5. LIMITATIONS

A relatively small sample size and lack of fungal strain identification are the short comings of this study. Conclusions & observations

- Trichloroacetic acid peel is a cheap, available and useful option as an adjuvant in the treatment of resistant & recurrent dermatophytic infection.

- Increased incidence of T. cruris in adult females mostly due to direct contact (sexual contact with infected husband), 3 cases in this research were married.

- Increased incidence of T. corporis & cruris in children is mostly secondary to spread from parents due to indirect contact in the house hold (especially sharing the same toilet seat).

- Although flaring clinical presentation of the infection, many cases didn't show growth on fungal culture after 21-30 days (rate of positive culture were 25%) this needs more explanation, but emphasizes the importance of early treatment in classic clinical situation despite negative investigations.

Conflict of interest

The authors declare that there is no conflict of interest

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