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Emergence of Resistant Extensive Tinea Infections

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Abstract

Dermatophytosis is a contagious infection of the skin, nails, and hair that is spread by direct or indirect contact. There was a failure of standard therapy, resulting in the establishment of recurring and chronic dermatophytosis. The aim of study is to assess the extensive areas of tinea infections, the resistant and recurrent tinea infection, and the efficacy of antifungal drug on clinical cure. This is a type of cohort study was carried out at the outpatient clinic of the department of Dermatology of Salah Al-Deen General Hospital in Tikrit City in the period from October 2020 till June 2021 samples of 100 patients were included. Patients were given anti-fungal treatment and followed up for 3 months. Result is Trichophyton mentagrophytes were the most prevalent isolate. The study revealed statistically significant association between types of treatment and outcome (P = 0.001) Griseofulvin treatment had 33 % (no response) Itraconazole treatment has 9.6 % recurrent and 19.2 % no response. In conclusion the occurrence of atypical dermatophyte infections is rising and now become a Great Imitator. They become extremely extensive and late to diagnose.

Keywords: Dermatophytosis, Tinea, Recurrence, Resistance.

1. Introduction

Tinea is a group of superficial skin diseases produced by dermatophyte or ring worm organisms, which are molds belonging to three genera: trichophyton microsporum epidermophyton. These fungi or ringworm species can induce changes in the skin, hair, and nails. Now become a world-wide phenomenon, some were anthropophilic, but

others are zoophilic and geophilic arise in thesoil though they may sometimes affect humans [1]. The world-wide superficial mycotic infection prevalence has been detected to be 20% – 25 % in 2015 according to the World Health Organization. In the past seven and eight years, there has been an increase in recurrent, difficult to treat and chronic dermatophytosis. These modifications may lead to the complex interaction of elements of the host, agent, and environment [2]. Dermatophytes penetrate keratinized tissues by a combined enzymatic and physical attack on host tissues. They have been shown to produce enzymes, such as keratinases. Infection is transmitted by arthroconidia, spores formed by segmentation of fungal filaments (hyphae) that adhere to the skin, germinate, and invade the stratum corneum [3]. Usually, topical antifungals are the first-choice treatment for patients with recently diagnosed, separated cutaneous dermatophyte infections like tinea corporis, tinea cruris, and tinea pedis. Infections involving extensive areas of skin, hairy places other than the scalp (e.g., tinea barbae), or infections combined with severe allergic responses also require oral medication. Tinea manuum, capitis, and unguium are commonly treated with systemic antifungal drug. However, recently, these dermatophyte infections have become resistant to topical antifungals therapy which may possibly be due to antifungal resistance [4]. The most prescribed antifungal medications are Griseofulvin this antibiotic is extracted from a variety of Penicillium species and is used to treat fungal infections. It inhibits nuclear division by binding to microtubular proteins, making it fungistatic, Azoles are synthetic drugs that work by preventing fungal cytochrome P450 enzymes from producing ergosterol. Ergosterol is a component of the fungal cell membrane that is needed for survival and Allylamines are synthetic compounds that prevent the formation of ergosterol in the cell membrane by inhibiting squalene epoxidase, In vitro, they have a wide spectrum of action [5]. The aim of this study is to analyze the resistance pattern of patients with recalcitrant dermatophytosis.

2. Patients and methods

Non-Interventional prospective cohort study has been carried out at outpatient clinic of Dermatology of Salah Al Deen General Hospital & some private clinics in Tikrit City from 1st October 2020 to 30th June 2021. This study includes a randomly selected sample male and female patients suffering from clinically appearing dermatophytosis.

Data were collected through an organized questionnaire covering patient's sociodemographic information and information about the disease including duration, site of lesion, signs and symptoms, size of lesion and associated disease, and drug history. A cutaneous examination with detailed history taken from the patient. The diagnosis confirmed by KOH examination for the clinically suspected cases. The laboratory Tests: HbA1C, KOH mount test, and culture (fungal- growth media) were done for all patients. After taking all the information and tests systemic and topical antifungal medication was administered to patients and followed up was done every two weeks to check the patient's responses. Antifungal medications were given (systemic + topical or topical only). We gave single systemic medication (itraconazole) 100 mg per day from four to six weeks, except for some patient (children or adult with tinea capitis), given Griseofulvin 10-20 mg / kg / day for 2months. Topical medication (imidazole) (1 × 2) from two to four weeks, for newly diagnosed or who have no other comorbidity. Then patients follow up was done every two weeks to check patient's response which was classified as: 1st: complete healing (no signs or symptoms of infection), 2nd: incomplete healing; infection persist after six to eight weeks of continuous treatment, 3rd: recurrent; the occurrence of infection a few weeks after cessation of anti-fungal treatment [6], 4th: no response; persistence of infection after 12 weeks of continuous treatment. Written informed consent was taken from all the patients. They are informed that contribution to the study is voluntary, and they can withdraw from the study after having agreed to participate. Data collection was kept confidential and not disclosed except for study purposes.

3. Results

In the current study, 38 patients (38 %) were males with mean age of (26.1 ± 15.9 years) and 62 (62 %) were females with mean age of (24.9 ± 15.5) years. Patients' age ranged from (2 – 60) years with mean ± SD is 25.4 ± 15.6 with most prevalent of age group were (26 - 45 years) and less than 15 years (31 % and 30 % respectively). While 53 (53 %) were living in urban area, among which 33 (33 %) were females and 20 (20 %) were males, whereas 47 (47 %) were dwelling in rural area of which 29 (29 %) were females and 18 (18 %) were males. The occupation of study groups was highly present among the student patients 23 (23 %), farmers 19 (19 %) and 17 (17%) were housewives as in table 1.

Table 1: Sociodemographic characteristics of study sample**.**

Variables			Frequency	Percent %
Gender	Male		38	38
	Female		62	62
Age category	<15 years		30	30
	15-25 years		28	28
	26-45 years		31	31
	> 45 years		11	11
Residency	Rural	Female	29	29
		Male	18	18
	Urban	Female	33	33
		Male	20	20
Marital status	Married		56	56
	Unmarried		44	44
Occupation	Child-adolescent		16	16
	Farmer		19	19
	Housewife		17	17
	Retired		4	4
	Soldier		5	5
	Student		23	23
	Worker		16	16

The results of the current study showed 87 % of participant have positive scraping test, 86 % have positive culture and the most common types of fungi according to culture examination were T. mentagrophyte, T. rubrum, M. canis and T. verrucosum (30 %,19 %,12 % and 8 % respectively), while only 14% had negative culture result. The highest distribution was among extremities 37 %, trunk (25 %) and 17 (17 %) in multiple areas in the body (extensive area of the body), with more than two third of cases, having duration of disease of less than six months also the results found 55 % of patient. have size of lesion more than 10 cm2. While 79 % of cases have less than ten lesions and 21 % have more than ten. Moreover, the most prevalent patients (68 %) didn't have a history of antifungal drugs, and only 29 % of cases were used previously (topical

+systemic) as shown in table 2. Signs and symptoms were as follow, itching (pruritus) was the commonest symptom 74 (74 %), scales 82 (82 %), burning 30 (30 %), erythema 68 (68 %), hypopigmentation and hyperpigmentation each 6 %, scar 4 (4 %). as shown in table 3.

Table 2: Distribution of study sample according to skin lesion characteristic.

Variables		Frequency	Percent %
Scrapping test	-ve	13	13
	+ve	87	87
Culture	-ve	14	14
	(+ve) *E. floccosum*	5	5
	(+ve) *M. audouinii*	5	5
	(+ve) *M. canis*	12	12
	(+ve) *M. gypseum*	4	4
	(+ve) *T. verrucosum*	8	8
	(+ve) *T. violaceum*	3	3
	(+ve) *T. mentagrophyte*	30	30
	(+ve) *T. rubrum*	19	19
Site of lesion	Extremities	37	37
	Trunk	25	25
	Multiple	17	17
	Face	8	8
	Scalp	7	7
	Nail	6	6
Duration	<6 month	69	69
	≥6 month	31	31
Surface area	<10 cm^2	45	45
	≥10 cm^2	55	55
Number of lesions	<10	79	79
	≥10	21	21
Previous Drug (antifungal)			
	No	68	68
	Topical	3	3
	Topical +systemic	29	29

Table 3: Distribution of study samples according to symptoms and signs.

Variables		Frequency	Percent %
Symptoms and signs	Scaly	82	82
	Itching (pruritus)	74	74
	Erythema	68	68
	Burning	30	30
	Hypo-pigmentation	6	6
	Hyper-pigmentation	6	6
	Scar	4	4

In current study the results found 76 % of study sample did not have any drug history while 19% used topical steroid, one patient used Antihypertensive, one patient used Aspirin and one patient used Pentostam. Regarding to types of treatment used during the study were Itraconazole, Griseofulvin and Topical antifungal (52 %, 15 % and 33 % respectively). All the included cases received topical and systemic antifungal treatment then they are reexamined after two to three weeks from the last visit 66 (66 %) of cases respond excellently to antifungal therapy and 16 (16 %) of cases didn't respond, 13 (13 %) were incomplete 5 (5 %) with recurrence after few weeks of remission table 4.

Table 4: Distribution of study sample according to treatment and outcome.

Variables		Frequency	Percent %
Drug History	Anti- hypertensive	1	1
	Aspirin	1	1
	Contraceptive pill	1	1
	Diovan	1	1
	Non	76	76
	Pentostam	1	1
	Topical steroid	19	19
Treatment	Griseofulvin	15	15
	Itraconazole	52	52
	Topical antifungal	33	33
outcome	Healing	66	66
	Incomplete	13	13
	No response	16	16
	Recurrence	5	5

The most prevalent age category was (26-45 years), with the most no response present (25.8 %), while the highest percent of healing was among less than fifteen year (83.3 %), also the highest percent of recurrent disease recorded at age more than 45 years. and without any statically significant association between age and result outcome (p = 0.068). regarding to sex correlation with result outcome the study did not found any statically difference (p = 0.440), as shown in table 5.

Table 5: Relation between (age, gender) and treatment result (outcome).

Age	Healing	Incomplete	No response	Recurrent	Total	P value
<15 years	25	2	3	0	30	
	83.30 %	6.70 %	10.00 %	0.00 %	100 %	
15-25 years	16	8	3	1	28	
	57.10 %	28.60 %	10.70 %	3.60 %	100 %	
26-45 years	18	3	8	2	31	
	58.10 %	9.70 %	25.80 %	6.50 %	100 %	
>45 years	7	0	2	2	11	0.068
	63.60 %	0.00 %	18.20 %	18.20 %	100 %	
Gender	**Healing**	**Incomplete**	**No response**	**Recurrent**	**Total**	
F	39	9	12	2	62	
	62.90 %	14.50 %	19.40 %	3.20 %	100 %	
M	27	4	4	3	38	
	71.10 %	10.50 %	10.50 %	7.90 %	100 %	0.440

In current study there are statically significant association between types of treatment and outcome (p = 0.001), with highest healing percent recorded in topical treatment and without any recurrent while Griseofulvin treatment had more than 33 % (no response) also, Itraconazole. treatment has 9.6 % recurrent and 19.2 % nonresponse table 6.

Table 6: Relation between (types of drugs) and treatment result (outcome).

Treatment	Healing	Incomplete	No response	Recurrent	Total	P value
Griseofulvin	10	0	5	0	15	
(Gr)	66.70 %	0.00 %	33.30 %	0.00 %	100 %	
Itraconazole	25	12	10	5	52	0.001
(Itra.)	48.10 %	23.10 %	19.20 %	9.60 %	100 %	
Topical	31	1	1	0	33	
	93.90 %	3.00 %	3.00 %	0.00 %	100 %	

Table 7 showed no statistically significant association between types of occupation and residence and outcome (p = 0.112 and 0.069 respectively). Healing among children, farmer, and student while more recurrent among retired and solider.

Table 7: Study sample according to sociodemographic characteristic and result (outcome).

Occupation	Healing	Incomplete	No response	Recurrent	Total	P value
Child	12	1	3	0	16	
	75.00 %	6.30 %	18.80 %	0.00 %	100 %	
Farmer	14	2	2	1	19	
	73.70 %	10.50 %	10.50 %	5.30 %	100 %	
Housewife	7	3	7	0	17	
	41.20 %	17.60 %	41.20 %	0.00 %	100 %	0.112
Retired	3	0	0	1	4	
	75.00 %	0.00 %	0.00 %	25.00 %	100 %	
Soldier	1	2	1	1	5	
	20.00 %	40.00 %	20.00 %	20.00 %	100 %	
Student	18	3	1	1	23	
	78.30 %	13.00 %	4.30 %	4.30 %	100 %	
Worker	11	2	2	1	16	
	68.80 %	12.50 %	12.50 %	6.30 %	100 %	
Residence	**Healing**	**Incomplete**	**No response**	**Recurrent**	**Total**	
Rural	31	4	7	5	47	
	66.00 %	8.50 %	14.90 %	10.60 %	100 %	0.069
Urban	35	9	9	0	53	
	66.00 %	17.00 %	17.00 %	0.00 %	100 %	

The current study showed the highest percentage (100 %) of healing among two types of fungus (E. floccosum and M.gypseum) and without (no response and recurrent), while T. mentagrophyte have more percentage of (no response) 26.7 %. But T.violaceum recorded 33.3 % recurrent outcome moreover there isn't significant association between types of fungus and outcome (p = 0.139). Also, there are statistically significant association between duration of lesion, number of lesion and size of the lesion (p value = 0.03, 0.042 and 0.026) as shown in table 8.

Table 8: Sample study according to types of fungus, skin lesion characteristics, and result.

Culture	Healing	Incomplete	No response	Recurrent	Total	P value
E. floccosum	5	0	0	0	5	
	100 %	0.00 %	0.00 %	0.00 %	100 %	
M. audouinii	3	0	2	0	5	
	60.00 %	0.00 %	40.00 %	0.00 %	100 %	
M. canis	11	1	0	0	12	
	91.70 %	8.30 %	0.00 %	0.00 %	100 %	
M. gypseum	4	0	0	0	4	0.139
	100 %	0.00 %	0.00 %	0.00 %	100 %	
T.verrucosum	6	1	1	0	8	
	75.00 %	12.50 %	12.50 %	0.00 %	100 %	
T.violaceum	2	0	0	1	3	
	66.70 %	0.00 %	0.00 %	33.30 %	100 %	
T. mentagrophyte	15	5	8	2	30	
	50.00 %	16.70 %	26.70 %	6.70 %	100 %	
T. rubrum	14	1	2	2	19	
	73.70 %	5.30 %	10.50 %	10.50 %	100 %	
Duration	**Healing**	**Incomplete**	**No response**	**Recurrent**	**Total**	**P value**
<6 month	49	10	6	4	69	
	71.0 %	14.5 %	8.7 %	5.8 %	100.0 %	0.030
≥6 month	17	3	10	1	31	
	54.8 %	9.7 %	32.3 %	3.2 %	100.0 %	
Size of lesion	**Healing**	**Incomplete**	**No response**	**Recurrent**	**Total**	**P value**
<10 cm^2	34	7	4	0	45	
	75.6 %	15.6 %	8.9 %	0.0 %	100.0 %	0.042
≥10 cm^2	32	6	12	5	55	
	58.2 %	10.9 %	21.8 %	9.1 %	100.0 %	
Number of lesions	**Healing**	**Incomplete**	**No response**	**Recurrent**	**Total**	**P value**
<10	57	8	12	2	79	
	72.2 %	10.1 %	15.2 %	2.5 %	100.0 %	0.026
≥10	9	5	4	3	21	
	42.9 %	23.8 %	19.0 %	14.3 %	100.0 %	
Site of lesion	**Healing**	**Incomplete**	**No response**	**Recurrent**	**Total**	**P value**
Extremities	29	3	4	1	37	
	78.4 %	8.1 %	10.8 %	2.7 %	100.0 %	
Face	5	3	0	0	8	
	62.5 %	37.5 %	0.0 %	0.0 %	100.0 %	0.063
Multiple area	7	4	4	2	17	
	41.2 %	23.5 %	23.5 %	11.8 %	100.0 %	
Nail	1	2	3	0	6	
	16.7 %	33.3 %	50.0 %	0.0 %	100.0 %	
Scalp	7	0	0	0	7	
	100.0 %	0.0 %	0.0 %	0.0 %	100.0 %	
Trunk	17	1	5	2	25	
	68.0 %	4.0 %	20.0 %	8.0 %	100.0 %	

4. Discussion

The result of the current study showed 87 % of participant have positive scraping test (KOH), and 13 % a negative. It might be explained by small sample size or by using of different types of medications by patients prior to the study, The most common types of fungi according to culture examination were T. mentagrophyte, T. rubrum, M. canis and T. verrucosum (30 %, 19 %, 12 % and 8% respectively). According to Rebollo et al in 2008, T. tonsurans has been the most prominent causal organism of tinea capitis in developed countries, while M. canis has been the most major pathogen in developing countries like Mexico, followed by T. tonsurans [7]. While Sharque et al 2020 in Iraq found that 63 patients with positive dermatophyte culture, 63 % T. mentagrophytes, 11 % M. canis, 10 % E. floccosum, 8 % T. rubrum, 3% T. violaceum [8]. This study is in accordance with our study where T. mentagrophytes 34.9 % is the most common species in Tikrit City. SHAMQI, A. J. in Iraq 2014 found that T. mentagrophytes 32 %, T. rubrum 15 %, M. canis 9% [9]. There has been a significant change in epidemiology recently, with T. mentagrophytes emerging as the most common pathogen, displacing T. rubrum [2]. The female predominance in the present study is like a study conducted by Pires CAA, et al study in (2014) [10]. This can be explained by the fact that females are more likely to seek. medical care [11]. In current study found more than two third of cases have a duration of disease of less than 6 month. This result like study conducted by Hosthota A et al. [12], that found (52 %) of cases had a duration of dermatophytoses lower than 6 months. In contrast to Agarwal et al. [13], reported 62.5 % cases having lesions > 6 months. This suggests that in present study there were more patients who were newly infected duration. In the current study the most prevalent patient's management is a combination (Itraconazole + topical) (52 %) and 33 % used topical treatment while 15 % used combination (Griseofulvin + topical). And in our result found the highest percentage of healing was among patients that treatment by topical with statistically significant association. Pires CAA et al. [10] found that 17.5 % used topical treatment and 17.5 % used systemic treatment while 62 % used combination treatment and without any statically significant association between types of treatment and healing response. Another study done by Dias MFRG et al. [14] found the complete cure rate was 90-100 % among itraconazole treatment while 86 % in griseofulvin therapy.in our study the cure rate

among patients who treatment by griseofulvin was 66.7 % this result is nearly like study conducted by Deng et al. [15] and Ely JW et al. [16] that reported cure rates (85 % and 92 % respectively). While another research by Elewski et al. [17] 2008 and Mikaeili A et al. [18] reported (39 % and 55 % respectively). Regarding the cure rate among patients treated with itraconazole, the current study scored 48% while Sultana R [19] 23.53 % of the sample was cured. The possible causes of this variation may be because of the difference between the study sample and severity of cases or maybe resistance to the antifungal drug by dermatophytes. Studies on drug resistance have not correlated with clinical findings in a substantial way [20-21]. Regarding the incomplete response in patient using Itraconazole (23.1 %) of cases show some improvement in clinical signs and symptoms) but no complete cure, also (19.2 %) of patients show no response, and 9.6 % show recurrent. This agrees with many studies conducted in India which show emergence of resistant tinea where Gupta. A. found that relapse 20 % of cases after antimycotic drug use, also Moriarty et.al. enlist therapy failure due to common causes such as inadequate compliance to medication, Infection relapse, emergence of drug resistance, misdiagnosis, and infection with rare species [22-23]. Dermatophytes with increased minimum inhibition concentrations to azole have been recorded in the last year [24]. As a result of these chronic and relapsing cases, we notice an increase in the number of cases with tinea faciei and tinea pseudoimbricata in our study. In patient infected with T. mentagrophyte, 50 % were healed and another 50 % were distributed as no response, incomplete, or recurrence, 26.70 %, 16.79 %, 6.70 % respectively.

5. Conclusion

The occurrence of atypical dermatophyte infections is rising and now become a great imitator. Late diagnosis of the disease because it is not managed by dermatologists alone, extensive disease, atypical presentations, and extension of the disease into the scalp and face are common. Identification of dermatophyte species is important to detect the source of infection. The optimal antifungal drug dosage and duration remain elusive and needs to increase the dose and duration of antifungal drugs. Contagious rate of dermatophytosis now is rising, so must educate the patient about it.

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