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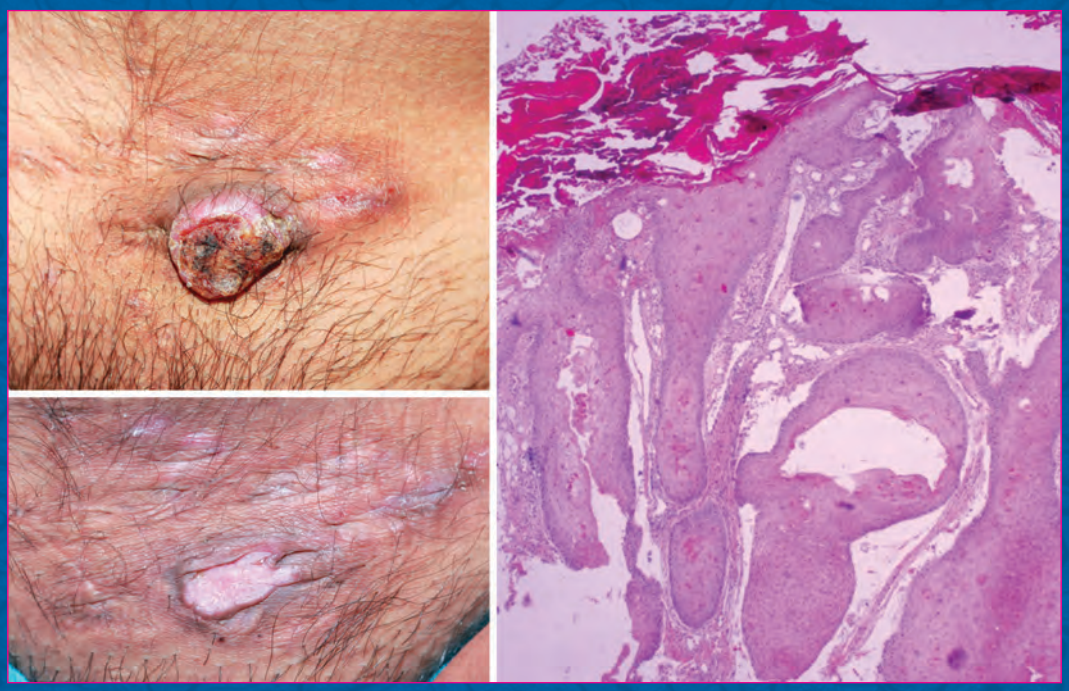

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Original Article

Randomized Control Trial of Itraconazole in the Treatment of Dermatophytosis: Comparison of Three Different Dose Regimens

Abhishek Chandrakant Lachure, Bhabani S. T. P. Singh, Bikash Ranjan Kar, Liza Mohapatra, Nibedita Dixit

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Abstract

Introduction: Dermatophytosis is a superficial fungal infection of keratinized tissue caused by dermatophytes. The use of itraconazole in the standard dose and duration is commonly resulting in treatment failure. **Aims and Objectives:** To compare the efficacy and safety of three different dosage regimens of itraconazole in the treatment of dermatophytosis. **Materials and Methods:** Patients were enrolled and randomly assigned to three different groups A, B, and C after obtaining the proper consent. For four weeks, patients in Groups A, B, and C received itraconazole 100 mg once daily, 200 mg once daily, and 5 mg/kg or 400 mg daily, whichever was lesser, in two divided doses, respectively. All patients were advised to use topical eberconazole cream twice daily and levocetirizine 5 mg daily. Potassium hydroxide (KOH), culture for fungus, complete blood count (CBC), and liver function test (LFT) were done at the baseline visit and repeated in 4 weeks. A clinical assessment was done at both visits. **Result:** KOH was negative for fungal elements in 21.4%, 19%, and 17% of patients in groups A, B, and C respectively, after the completion of therapy. The culture was negative for fungal elements in 19%, 17.5%, and 19.5% of patients in groups A, B, and C respectively, post-therapy. At the end of four weeks, there was a statistically significant decrease in lesion count, body surface area involvement, erythema, and itching within all three groups. However, after 4 weeks of therapy, there was no significant difference in clinical outcome or mycological status among the three groups. **Conclusion:** Our study concludes that the higher dose of itraconazole does not prove to be more efficacious and has no added advantage over the conventional dose in the treatment of dermatophytosis at the end of four weeks. Therefore, we suggest for long-term (more than 4 weeks) itraconazole therapy with the conventional dose to achieve an adequate cure.

Keywords: Antifungal, azoles, different dose regimens, efficacy, safety, superficial fungal infection

Introduction

Dermatophytosis is a superficial fungal infection of keratinized tissue caused by dermatophytes. The disease has a significant negative impact on social, psychological, and occupational health.[1] Studies have shown an increasing burden of dermatophytosis in the general population.[2] There is an epidemic of recurrent and chronic dermatophytosis in India.[3] Among the systemic antifungals, itraconazole is the most commonly used drug in the treatment of dermatophytosis. The textbook recommended dose of itraconazole is 100 mg per day for 2–4 weeks.[4] The doses of itraconazole have also been mentioned as 200 mg per day for 1 week.[5] However, failure of treatment is being increasingly seen with the use of itraconazole in conventional doses and duration. An inappropriate dose or duration of itraconazole may lead to a partial response, rapid recurrence of infection, and the development of drug resistance.[6] The risk of adverse effects due to the use of higher doses of itraconazole also

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exists. Under the prevailing conditions, there is a paucity of literature about the adequate and appropriate dose of itraconazole in tinea. Hence, this study was designed to compare the efficacy and safety of three different dose regimens of itraconazole in the treatment of dermatophytosis.

Aims and Objectives

1. To compare the efficacy of three different dosage regimens of itraconazole in the treatment of dermatophytosis. (100 mg once daily vs 200 mg once daily vs 5 mg/kg or 400 mg daily, whichever is lesser).
2. To compare the safety of three different dosage regimens of itraconazole in the treatment of dermatophytosis.

Materials and Methods

Sample size

The mycological cure rate of dermatophytosis was 70% with a dose of itraconazole 100 mg daily,[7] in comparison to 92% with itraconazole 200 mg daily.[6] We wanted to estimate and compare the cure rate with 400 mg or 5 mg/kg itraconazole. At a 95% confidence interval, with an estimated difference in the proportion of cure rate between the treatment groups of 22%, with an alpha error of 5%, and a beta error of 20%; the sample size was determined to be 35 in each arm. Considering a dropout rate or loss to follow-up of 20%, the sample size was inflated to 42 in each arm. A sample size of 126 (42 in each group) was calculated using the software "P-value: A statistical tool" by Dr. Kusum Gaur.[8] Ethics committee (Ref No/DMR/IMS.SH/SOA/180342) approval was obtained to carry out this study. The trial was registered in the clinical trial registry of India with the CTRI registration number (CTRI/2020/08/027063). The study was carried out from September 2020 to October 2021.

Inclusion criteria

1. All naive cases of dermatophytosis.
2. Positive cases with fungal hyphae on potassium hydroxide (KOH) test.
3. Patients aged 18 to 60 years.
4. Previously treated cases but off treatment from topical/systemic antifungal since last 4 weeks.

Exclusion criteria

1. Pregnant or lactating patient.
2. Patients with a history of diabetes or immunosuppression.
3. Patients taking drugs that interfere with itraconazole metabolism.
4. History of hepatic and renal impairment.
5. Known cases of congestive heart failure

Methodology

Detailed consent in both English and the local language was taken from the patient before enrolling them in the study. Then, the patients were randomly assigned to different groups based on a computer-generated random number table. For four weeks, group A patients received 100 mg of itraconazole once daily, group B patients received 100 mg twice daily, and group C patients received 5 mg/kg or 400 mg daily (whichever was less) in two divided doses. All the participants were prescribed topical eberconazole cream to be applied twice daily on the affected area and a tablet of levocetirizine 5 mg daily for 4 weeks. All patient samples (skin scraping) were sent for potassium hydroxide (KOH) and culture, along with a complete blood count (CBC) and liver function test (LFT) at baseline and again at the end of the 4th week [Figure 1].

Assessment tool

Direct microscopic examination (KOH), culture, and clinical photographs of both visits were compared. Grading of clinical parameters was done by the measurement of body surface area (BSA) involved, while the erythema was measured at both visits on a scale of 0–3 (0-absent, 1-mild, 2-moderate, and 3-severe), and the itching was quantified by the visual analog scale (VAS) (0–10).

Statistics

The information was entered into Microsoft Excel 2007 and analyzed using SPSS version 27 (IBM corporation, Armonk, New York). The categorical variables were expressed in terms of their numbers and percentages, whereas, continuous variables were expressed in terms of their mean and standard deviation. The association of two categorical variables among the groups was obtained using the Chi-square test, whereas, within the groups, an association was obtained using McNemar's test. An association between continuous variables between two independent groups was obtained using an unpaired t-test. A P-value of less than 0.05 was considered statistically significant.

Result

The demographic profile (age/gender) was comparable among all the participants. The mean age ± SD (in terms of years) was 32.88 ± 9.26, 34.74 ± 10.16, and 37.17 ± 6.18 in groups A, B, and C respectively (P = 0.081). Male to female ratio in groups A, B and C was 19:23, 26:16, and 27:15 respectively. The gender comparison between the three groups was comparable (P = 0.196). However, the duration of infection among the three groups was not comparable. The mean duration ± SD (in terms of days) of infection in group B was 88.10 ± 71.4 while in groups A and C it was 49.93 ± 40.21 and 49.40 ± 33.83 respectively (p-value = 0.001). Clinical features such as the number of lesions, body surface area involvement, and itching as scored

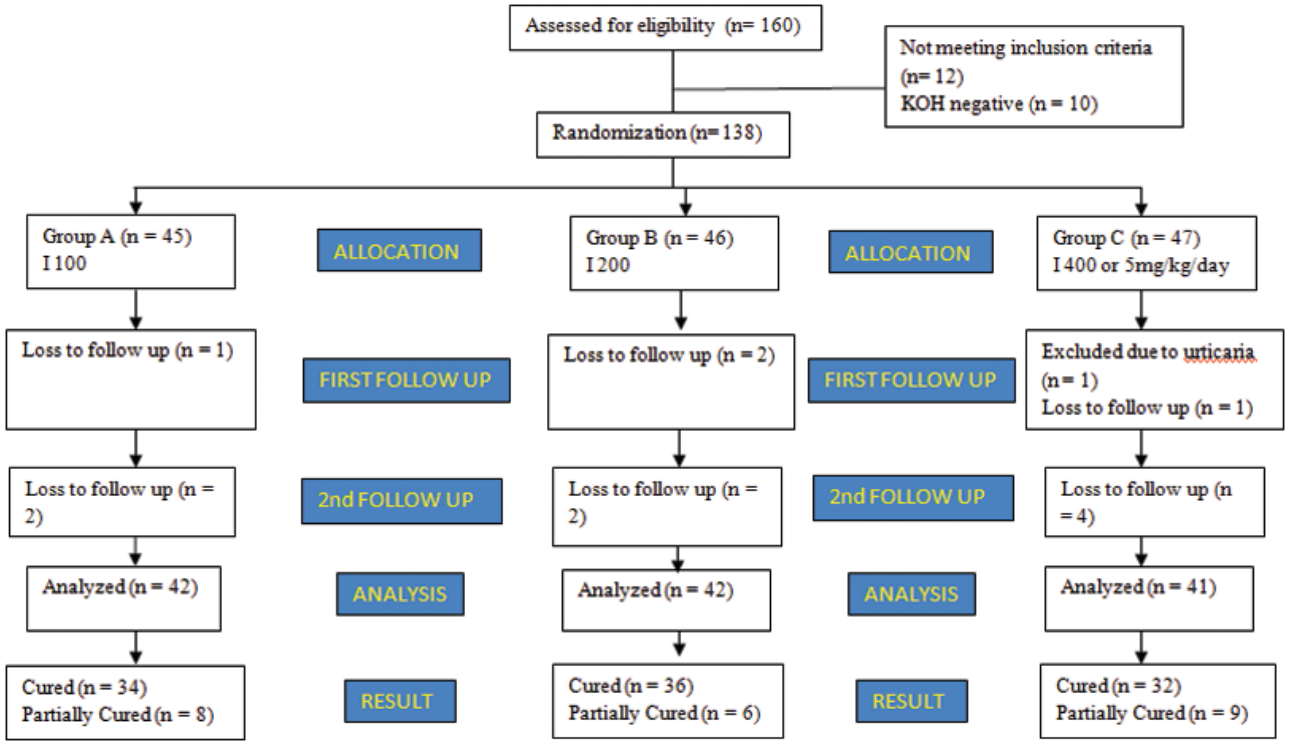

Figure 1: Flow chart depicting passage of participants in the study

on VAS were all comparable among the three groups at the baseline visit [Table 1]. Grading of itching and erythema at the baseline visit was also comparable among the three groups, with p-values of 0.343 and 0.083, respectively.

The decrease in lesion count from the baseline visit was statistically significant in each group at the end of the 4th week with p = < 0.001 [Table 1]. There was no significant difference in the number of lesions at the end of the 4th week when compared among the three groups [Table 1].

There was a statistically significant decrement in the BSA involvement in patients at the end of the 4th week when compared to the baseline in each of the groups with p = < 0.001 [Table 1]. The statistical comparison of BSA involvement at 4 weeks was not significant across the three arms [Table 1].

There was a statistically significant improvement in the VAS of itching post-therapy in all three groups [Table 1]. However, after 4 weeks of therapy, the statistical comparison of VAS of itching was not significant among the three groups [Table 1].

The grading of itching was significantly improved in each group post-therapy, with p-values of 0.027, 0.001, and 0.012 in groups A, B, and C respectively. The grading of erythema also decreased significantly in each group at the end of the therapy with p values of 0.006, 0.006, and 0.004 in groups A, B, and C respectively. However, the inter-group comparison of improvement in the grading of itching (P = 0.53) and erythema (0.753) was not statistically significant, at the end of the intervention.

Table 1: Intra-group and Inter-group comparison of clinical parameters

Number of lesion	Group A	Group B	Group C	*P* value
Baseline	5.55 ± 2.00	6.52 ± 3.44	6.93 ± 3.41	0.103
F/U visit	1.83 ± 1.32	2.38 ± 1.86	2.27 ± 1.94	0.312
	F/U visit	**Baseline Vs F/U visit (*P* value)**		
Group A	1.83 ± 1.32	< 0.001		
Group B	2.38 ± 1.86	< 0.001		
Group C	2.27 ± 1.94	< 0.001		
Body Surface area	**Group A**	**Group B**	**Group C**	***P* value**
Baseline	3.71 ± 1.62	4.55 ± 2.93	4.20 ± 2.70	0.306
F/U visit	0.88 ± 0.83	0.93 ± 0.82	1.04 ± 1.24	0.747
	F/U visit	**Baseline Vs F/U visit (*P* value)**		
Group A	0.88 ± 0.83	< 0.001		
Group B	0.93 ± 0.82	< 0.001		
Group C	1.04 ± 1.24	< 0.001		
VAS of itching	**Group A**	**Group B**	**Group C**	***P* value**
Baseline	7.76 ± 1.36	7.95 ± 1.43	8.36 ± 1.01	0.097
F/U visit	3.00 ± 1.90	3.29 ± 2.06	3.51 ± 1.86	0.487
	F/U visit	**Baseline Vs F/U visit**		
Group A	3.00 ± 1.90	< 0.001		
Group B	3.29 ± 2.06	< 0.001		
Group C	3.51 ± 1.86	< 0.001		

Table 2: Intra-group comparison of KOH and culture

KOH results	Group A		Group B		Group C	
	Baseline	F/U visit	Baseline	F/U visit	Baseline	F/U visit
Positive	42 (100%)	33 (78.57%)	42 (100%)	34 (82.93%)	41 (100%)	34 (82.93%)
Negative	0 (0%)	9 (21.43%)	0 (0%)	7 (17.07%)	0 (0%)	7 (17.07%)
Baseline Vs F/U visit (p value)	0.006		0.023		0.012	
Culture status	**Group A**		**Group B**		**Group C**	
	Baseline	F/U visit	Baseline	F/U visit	Baseline	F/U visit
Positive	42 (100%)	34 (80.95%)	42 (100%)	35 (83.3%)	41 (100%)	33 (78.57%)
Negative	0 (0%)	8 (19.05%)	0 (0%)	7 (17.5%)	0 (0)	8 (19.51%)
Baseline Vs F/U visit (*p* value)	0.012		0.023		0.012	

Table 3: Inter-group comparison of KOH and culture after 4 weeks of therapy

	Group A	Group B	Group C	Total	*P* value
KOH result					
Positive	33 (78.57%)	34 (82.95%)	34 (82.93%)	101 (80.8%)	0.877
Negative	9 (21.43%)	8 (19.05%)	7 (17.07%)	24 (19.2%)	
Culture status					
Positive	34 (82.95%)	35 (83.33%)	33 (80.49%)	102 (81.6%)	0.965
Negative	8 (17.05%)	7 (16.67%)	8 (19.51%)	23 (18.4%)	

A significant number of patients tested negative for fungal elements on KOH smears at four weeks in each of the groups when compared with their baseline status. KOH was negative in 21.4%, 19%, and 17% of patients in groups A, B, and C respectively [Table 2]. There was no significant difference in the conversion of KOH status across the three groups after the completion of therapy, with $P = 0.877$ [Table 3].

There was a statistically significant conversion of culture status in all three groups. Skin scrapping did not yield any fungal growth in 19%, 17.5%, and 19.5% of patients in groups A, B, and C respectively after 4 weeks of therapy [Table 2]. But, the statistical comparison of the culture after 4 weeks of therapy among all three groups was not significant with $P = 0.965$ [Table 3].

In our study, one patient in group C developed urticaria (withdrawn from the study and treated with only oral antihistaminic) and one patient in group A developed an id reaction (treated with the short course oral steroid).

The most common site of persistence of lesions after the 4 weeks of therapy was the groin, followed by the buttock. The statistical comparison of the number of cases with persistent lesions after the therapy among the three groups was not significant.

After 4 weeks of therapy, there was no abnormal derangement of platelet levels in any of the participants. The platelet level at baseline and after 4 weeks of therapy in groups A and C showed a statistically significant decrease with p-value of 0.001 and 0.017 in groups A and C respectively. The decrease in the platelet count was within the physiological limit. There was no significant derangement of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels after 4 weeks of therapy in any of the participants at an individual level. But, the statistical comparison of SGPT level at baseline and after 4 weeks of therapy was significant within group C (without any clinical adverse outcome or any biological relevance), indicating a higher dose of itraconazole could lead to derangement of liver enzymes more frequently than the lower dose.

Discussion

Superficial dermatophytosis is considered the most common infective dermatosis in the world, affecting approximately 1/4th of the total world population. The ongoing epidemic of superficial dermatophytosis can be attributed to relapse, recurrence, as well as chronicity. Factors thought to be responsible for the rise in prevalence are inappropriate use of oral and topical antifungals, and rampant misuse of over-the-counter steroid containing mixed creams. In current times, antifungals in their standard doses and duration do not provide a complete cure.[9] According to an Indian study, itraconazole has shown higher clinical and mycological cure rates than terbinafine. With respect to terbinafine therapy, failure rate is high and a longer duration of treatment is required. Therefore, itraconazole is superior to terbinafine in the treatment of superficial fungal infections.[6]

In our study, 57.14% were males and 42.86% were females, with a male-to-female ratio of 1.3:1. This ratio was similar to the findings of previous studies, with a male-to-female ratio

of less than 2.[10-13] The higher prevalence of tinea in males could be explained by factors like increased indulgence in outdoor activities. This exposes them to environmental conditions favorable for the growth of fungus.[11] Higher percentage of patients (44.44%) were in the age group of 31 - 40 years, followed by 34.82%, 17.46%, and 2.38% in 18 - 30 years, 41 - 50 years, and 51 - 60 years respectively. This finding is corroborated by studies conducted by Janardan *et al.*, Singh *et al.* and Agarwal *et al.*[11-13] Such observation could be due to this age group of patients belonging to the working class people with more exposure to humidity and close contact at work. The mean age observed across various studies has been around 31–33 years, which is similar to our study.[10,11] 30.16% of patients were qualified below graduation, whereas 69.84% of patients were graduates or postgraduates, which corresponds to the finding of the study conducted by Kaur *et al.*[14] Similarly, a recent study showed that the majority of their patients had medium educational qualifications (60.20%).[10] Qualified patients, being more aware, and conscious, are motivated to seek medical care, thereby explaining our findings. In our study, a family history of dermatophytosis was present in 42.06% of patients, similar to findings published by Singh *et al.*[11] Dermatophytosis in the study participant was not associated with a positive family history (P value = 0.573). This indicates that the source of infection could be within the family as well as outside the family.

We divided the infection duration into four groups: group I (30 days), group II (30–90 days), group III (> 90 days to 180 days), and group IV (180 days). 73.02% of patients were in group II, followed by 12.5%, 10.32%, and 7.14% in groups I, IV, and III respectively. Chronic dermatophytosis is defined as an infection persisting for more than 6 months with or without recurrence after adequate treatment.[10] In our study, 10.32% of patients had chronic dermatophytosis. In a study, Agarwal *et al.* reported that 62.55% of patients were suffering from dermatophytic infection for more than 3 months.[15]A study in Eastern India revealed that 40.82% of patients were affected with dermatophytosis infection for more than 6 months.[1]

In our study, flexures were more commonly involved than extensors, with 69.84% of patients suffering from the infection in flexures. The majority of patients were suffering from tinea corporis et cruris (64.29%), followed by tinea corporis (19.84%) alone, and tinea cruris (15.87%) alone. The face was one of the affected sites in 7% of patients. In a study by Singh *et al.*, the most common variant detected was tinea corporis along with tinea cruris, followed by tinea corporis alone and tinea cruris alone.[11] Satyendra Singh *et al.* and Verma *et al.* also documented the most common type of tinea to be both tinea corporis et cruris followed by tinea cruris and tinea corporis.[9,10]

24.6% of patients had previously used some topical or oral therapy (1 month before being enrolled in the study) for the treatment of fungal infection. Singh *et al.* reported that 81.7% of patients in their study had previously used any form of medication to get rid of the fungal infection.[9] The patients usually apply steroid-containing mixed cream (due to its availability over the counter) to get symptomatic relief.

Approximately 20% of patients were cured after one month of therapy in all groups [Figures 2,4, and 6]. In

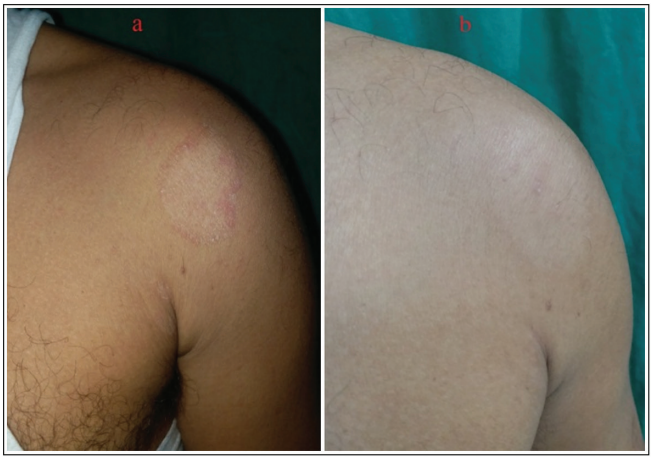

Figure 2: Patient of group A; (a) Lesion at baseline visit, (b) Lesion cleared after 4 weeks of therapy

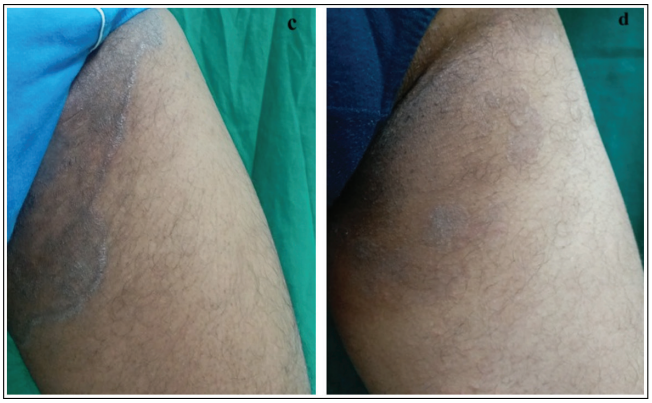

Figure 3: Patient of group A; (c) Lesion at baseline visit, (d) Lesion persisted after 4 weeks of therapy

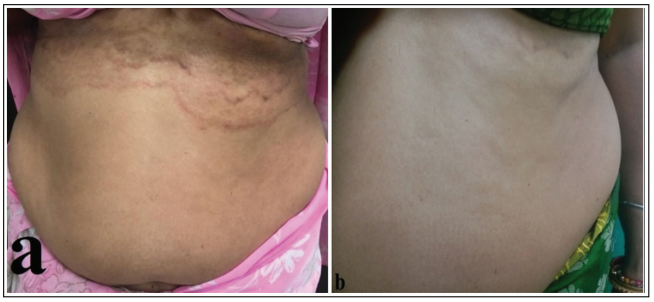

Figure 4: Patient of group B; (a) Lesion at baseline visit, (b) Lesion cleared after 4 weeks of therapy

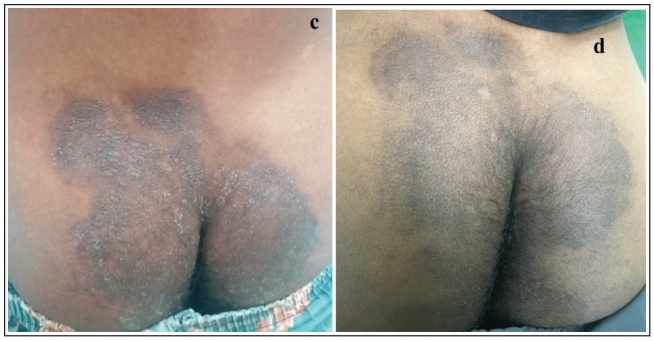

Figure 5: Patient of group B; (c) Lesion at baseline visit, (d) Lesion persisted after 4 weeks of therapy

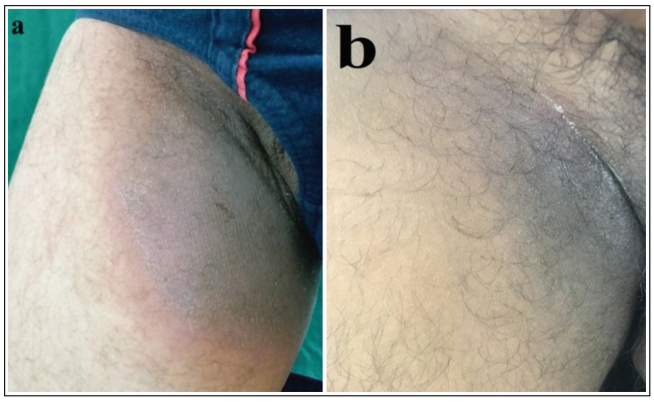

Figure 6: Patient of group C; (a) Lesion at baseline visit, (b) Lesion cleared after 4 weeks of therapy

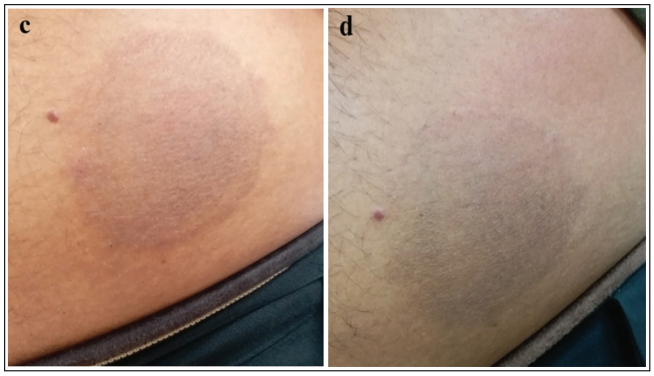

Figure 7: Patient of group C; (c) Lesion at baseline visit, (d) Lesion persisted after 4 weeks of therapy

comparison to the other groups, the remaining patients experienced post-treatment lesion persistence. The groin (47.83%) was the most common site of infection among those with persistent infection, followed by the buttock (43.83%) [Figures 3,5, and 7]. According to a Singh *et al.* study, 20% of patients showed lesion persistence even after being treated with different doses of itraconazole for 4–8 weeks.[9]

21.4%, 19%, and 17% of patients sampled for KOH were negative in the first, second, and third group respectively after 4 weeks of therapy. 19%, 17.5%, and 19.5% of patient's skin samples did not show any fungal growth on culture in the first, second, and third group respectively, after 4 weeks of therapy. The findings of KOH and culture in our study corroborate the finding of a study conducted by Satyendra Singh *et al.*, in which mycological cure was seen in 17% and 19.6% of patients with 200 mg and 400 mg of itraconazole respectively, after 4 weeks of therapy.[9] In a study by M. Haria *et al.*, the mycological cure rate was 65 to 84% after 1–3 weeks of therapy with 200 mg/day of itraconazole.[16] M. Haria conducted this study in 1996. According to H. Degreefe *et al.*'s study, the mycological cure rate was 92% after 4 weeks of 100 mg of itraconazole therapy.[17] However, it is not relevant to our study because this study, with a cure rate of 92%, was conducted in 1987. Frequent recurrences and relapses have been observed with short-term therapy of 100 mg itraconazole.[6] The findings in our study are in contrast to the observation put forth by Sardana *et al.*, that a higher plasma concentration (above 0.2 g/ml) is achieved with 400 mg of itraconazole, which helps to produce a better cure rate in dermatophytosis.[18] In a study, K Sardana and A Khurana reported that even after the use of variable or higher doses of itraconazole, adequate results are not being achieved.[19]

The most common fungal species detected in our study was *Trichophyton rubrum* (56.35%). Skin scraping showed growth of *Trichophyton mentagrophytes, Microsporum canis*, and *Epidermophyton* in 42%, 9%, and 4% of patients respectively. According to an eastern Indian study, the most common dermatophytes causing superficial fungal infection were found to be Trichophyton rubrum and Trichophyton mentagrophytes.[20] However, in another Eastern India study conducted by Singh *et al.*, *Trichophyton mentagrophytes* was found to be the most common fungal species causing dermatophytosis.[11] In a study conducted all over India, it was revealed that the strain responsible for the recent outbreak of superficial fungal infection is Trichophyton mentagrophytes.[21]

In our study, we did not find any significant abnormal derangement of liver enzymes or complete blood count in any of the patients among the three treatment arms at the end of 4th week. Liver enzyme abnormalities are rarely reported due to itraconazole alone. According to Satyendra Singh *et al.*, liver enzyme derangement was seen in only 1.27% of patients due to itraconazole.[9] Star Khoza *et al.* reported the incidence rate of hepatotoxicity as 1 per 10,000 due to itraconazole alone.[22]

Parameters like BSA involvement; total number of lesions; grading as well as the visual analog scale of itching, and the grading of erythema were studied to measure clinical cure in patients. For the mycological cure, skin scrapping for KOH and culture was done. There was no significant difference in the clinical and mycological cure among all three different regimens of itraconazole. Satyendra Singh also reported similar findings.[9]

Conclusion

Statistically significant clinical as well as mycological cure rates were observed with 100 mg, 200 mg, and 400 mg of itraconazole per day at the end of the 4th week. Though the mycological cure was significant with all the dose regimens, the percentage of patients attaining mycological cure was lower. There was no significant derangement of hematologic or hepatic enzyme levels with any of the doses. We propose the need for long-term (more than 4 weeks) itraconazole therapy to achieve adequate mycological cure along with the clinical cure. We conclude that there could be no added advantage of using high-dose itraconazole instead of conventional dose itraconazole in the current scenario of dermatophytosis.

Limitation

The duration of infection among the three groups was not comparable. Follow-up was not done after 4 weeks of study to monitor for the relapse of dermatophytosis.

Acknowledgement

Late Dr Tapaswini Tripathy (M.D), Assistant Professor, Dept. of DVL, IMS & SUM Hospital, SOA university, Bhubaneswar, Odisha, India. She contributed by helping us to achieve the required sample size and also by convincing the subjects to undergo the required investigation at every visit to ensure proper completion of the study.

Author's contribution

Abhishek Lachure – original manuscript writing, review and editing, data curation, literature search. Bhabani S.T.P Singh – original manuscript writing, data curation, statistical analysis, design. Bikash Kar – conceptualization, design, validation, reviewing. Liza Mohapatra – supervision, review and editing, validation. Nibedita Dixit – data curation, review and editing, statistical analysis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availibility statement

All the research data referred for this study can be directly accessed through the references provided at the end of the main manuscript.

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Original Article

Comparison of Efficacy of 40% Mandelic Acid with 30% Salicylic Acid Peels in Mild-to-Moderate Acne Vulgaris: A Randomized Study

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Abstract

Background: Chemical peel is a cosmetic procedure that is becoming a popular modality in treating acne vulgaris (AV). Mandelic acid (MA) is an upcoming peeling agent for AV due to its anti-inflammatory and antibacterial traits. Hence, it is worthwhile to appraise this newer agent's effectiveness and safety profile and compare it with a more traditional and established peeling agent, salicylic acid (SA), in the treatment of AV. **Aims:** The aim of this study was to compare the efficacy of 40% MA with 30% SA peels in south Indian patients suffering from mild-to-moderate facial AV. **Materials and Methods:** One hundred patients suffering from mild-to-moderate facial AV were distributed randomly into two groups of 50 each, with group A receiving 40% MA peel and group B receiving 30% SA peel at an interval of two weeks for six sessions. The duration of the study was twelve weeks. Clinical pictures and Michaelsson acne scores (MAS) were used to evaluate the effectiveness of treatment objectively. Adverse effects of both the peeling agents were also noted. **Statistical Analysis Used:** A value of $P \leq 0.05$ was considered significant. **Results:** Overall, there was no significant difference in the efficacy between the two peels. However, adverse effects were slightly higher with SA peel. **Conclusions:** The 40% MA peel was equally effective as 30% SA peel in mild-to-moderate facial AV. However, safety profile and tolerability were better in the MA peel group than the SA peel group.

Keywords: Acne vulgaris, chemical peeling, mandelic acid, Michaelsson acne score, salicylic acid

Introduction

Acne is a chronic inflammatory state of the pilosebaceous units, characterized by the emergence of comedones, erythematous papules and pustules, less often by nodules or pseudocysts. In the etiology of acne vulgaris, multiple factors play a role, determining the severity of the disease. Specific factors that may precipitate acne include genetic and environmental factors like diet, menstruation, emotional stress and cosmetics. The main factors responsible for the pathogenesis are increased sebum production, an abnormality of microbial flora, cornification of the pilosebaceous duct, production of inflammation and increased androgen levels. The severity of acne is associated with the degree of seborrhea, which is directly dependant on the extent and rate of growth of sebaceous glands, which is under the direction of androgens.[1] Acne affects 80% of individuals between puberty and 30 years of age.[2] It was also recorded in 54% of women and 40% of men over 25 years.[3] Non-inflamed lesions, the comedones, are either open comedones (blackheads) or closed comedones (whiteheads)—inflammatory lesions, perhaps superficial or deep, include papules, pustules and nodules. A microbial etiology of acne has been suggested since the beginning of the last century. There is considerable evidence that indicates that micro-organism, particularly *Cutibacterium acne or*

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Propionibacterium acne, is essential in the pathogenesis of acne vulgaris. However, it is still unsure whether *P. acne* is a causal agent in developing non-inflamed or inflamed acne lesions. Various treatment modalities like topical, systemic antibacterial, sebostatics, retinoids have been used as the treatment modalities for acne, and nowadays, dermatologists seek to employ new technologies in acne care like chemical peeling.[4] It's the application of the chemical agents on the skin that causes controlled destruction of the portion or entire epidermis with or without dermis leading to shedding and eliminating superficial lesions followed by restoration of new epidermal and dermal tissues.[5] Despite the advent of more contemporary techniques and LASER, peeling is still considered a simple procedure, requiring hardly any instrumentation to rejuvenate the skin.[5] Because of the resurfacing of the epidermal layer, the melanin content is declined, and it is more evenly distributed, improving hyperpigmentation.[6] SA is a β-hydroxy acid. SA has keratolytic properties as it solubilizes intracellular cement. Its lipid solubility allows the interaction with multilamellar frameworks encircling the keratinocytes in the stratum corneum and hair follicle, thereby showing follicular atrophy and comedolytic action inside the sebaceous unit.[7] "So, it is beneficial in comedonal and inflammatory acne.[8] MA is an 8-carbon alpha hydroxyl acid (AHA) which is named after German "Mandel", meaning almond and acquired from hydrolysis of an extract of bitter almonds. It has a high melting point, is partially soluble in water, and is freely soluble in isopropyl and ethyl alcohol.[9] It causes the dissolution of intercellular cement substances, stimulates collagen synthesis and promotes cellular regeneration.

Aim and Methods

Aim

This study was aimed at comparing the efficacy of 40% MA with 30% SA peels in mild-to-moderate acne vulgaris.

Methods

This was a prospective comparative study. One hundred patients of both genders with mild-to-moderate acne in the age group 15 to 45 years were included in the study. They were divided into two groups, 50 each; Stratified randomization was done using computer-generated random numbers into two groups (Group A 40% MA and Group B 30% SA). The study was done for a period of two years from January 2020 to December 2021.

Pregnant and lactating women, patients with history of hypersensitivity to SA or MA, patients with severe acne vulgaris (Grades III and IV), patients with hypertrophic scars or keloids, active infection (such as herpes simplex infection, open acne cysts), and patients who have received isotretinoin for during the last 6 months were excluded from the study.

Group A patients were treated with 40% MA every 14 days for six sessions. Group B patients were treated with 30% SA peel every 14 days for six sessions. Sensitive areas like the inner canthus of the eyes and nasolabial folds were protected with Vaseline. After degreasing with acetone, the corresponding peel was applied on the face starting from forehead, right cheek, nose, left cheek and chin in that order. Feathering strokes were used at the edges to blend with the surrounding skin. The end point for MA peel was erythema and for SA peel pseudo frosting or five minutes whichever ever occurred first. The procedure was concluded with face washing with tap water.

Both Group A and Group B Patients were advised to protect themselves from sunlight by using sunscreen regularly at daytime, at least until the study gets over. Results were assessed based on serial photographs, clinical improvement. Michaelsson acne scores (MAS) were used to evaluate the efficacy of therapy. The following graded scale was used for assessing objectively the progress: excellent (76%–100%), good (51%–75%), fair (26%–50%), and poor (0%–25%).[10]

The clinical findings and results were recorded in the pre-designed proforma for analysis and interpretation of data. Efficacy of the treatment based on total lesion count reduction (by using MAS Score), and adverse effects (erythema/dryness/pruritus or burning) were noted.

Statistical analysis

Categorical variables were summarized as the frequency with percentage, and continuous variables were summarized as mean. Fisher's exact test or chi-square test was applied to analyze the data. A value of $P \leq 0.05$ was considered significant.

Results

At the end of 12 weeks of peeling sessions the grading of improvement in acne from the baseline was assessed in each group using MAS score. More than 75% decrease in MAS score from the baseline was graded as excellent improvement; A 51 to 75% decrease was Graded as good improvement; A 26 to 50% decrease was Graded as fair improvement and less than 25% decrease in MAS score Graded as poor improvement.

Group A (40% MA peel)

Among 50 participants in Group A, 31 (62%) showed excellent improvement in their acne score of which 10 (20%) had Grade I acne and 21 (42%) had Grade II acne before treatment. Good improvement was noted in 17 participants (34%) of which 8 (16%) had Grade I acne and 9 (18%) had Grade II acne. Only two participants (4%) showed Fair improvement that were having Grade I acne. None showed Poor improvement [Table 1].

Group B (30% SA peel)

Among 50 participants in group B 22 (44%) showed excellent improvement in their acne score of which 3 (6%) had Grade I acne and 19 (38%) had Grade II acne before treatment. Good improvement was noted in 27 participants (54%) of which 6 (12%) had Grade I acne and 21 (42%) had Grade II acne. Only one participant (2%) showed Fair improvement that was having Grade I acne. None showed Poor improvement [Table 2].

Comparison of percentage of improvement in different grades of acne between 40% MA peel and 30% SA peel

Table 3 shows the comparison of percentage of improvement in different grades of acne with 40% MA peel and 30% SA peel. Patients with mild acne (Grade 1) who were treated with 40% MA showed good improvement in 16% of the patients. On the other hand, 12% of the patients with mild acne who were treated with 30% SA peel showed good improvement. Patients with moderate acne (Grade II) who were treated with 40% MA showed good improvement in 18% of the patients. On the other hand, 42% of the patients with grade II acne that were treated with 30% SA peel showed good improvement [Table 3 and Figures 1–4].

Improvement in mean MAS score from baseline to end of the study was more or less similar in both Group A and Group B indicating both MA peel and SA peel are equally effective in Grade I and Grade II acne vulgaris [Tables 4 and 5].

There was no statistically significant difference in the efficacy between the two Groups in terms of mean MAS score and mean percentage improvement.

Table 1: Percentage of improvement in different grades of acne with 40% MA peel

Percentage of improvement	Grade I acne	Grade II acne	Total *N* (%)
No change	0	0	0
0%–25% (poor)	0	0	0
26%–50% (fair)	2 (4%)	0	2 (4%)
51%–75% (good)	8 (16%)	9 (18%)	17 (34%)
76%–100% (excellent)	10 (20%)	21 (42%)	31 (62%)
Total	20 (40%)	30 (60%)	50 (100%)

Table 2: Percentage of improvement in different grades of acne with 30% SA peel

Percentage of improvement	Grade I acne	Grade II acne	Total *N* (%)
No change	0	0	0
0%–25% (poor)	0	0	0
26%–50% (fair)	1 (2%)	0	1 (2%)
51%–75% (good)	6 (12%)	21 (42%)	27 (54%)
76%–100% (excellent)	3 (6%)	19 (38%)	22 (44%)
Total	10 (20%)	40 (80%)	50 (100%)

Table 3: Comparison of percentage of improvement in different grades of acne between 40% MA peel and 30% SA peel

Percentage of improvement	40% MA peel Group A		30% SA peel Group B		*P* Value
	Grade 1	Grade 2	Grade 1	Grade 2	
No change	0	0	0	0	
0%–25% (poor)	0	0	0	0	0.044
26%–50% (fair)	2(4%)	0	1(2%)	0	
51%–75% (good)	8(16%)	9(18%)	6(12%)	21(42%)	
70%–100% (excellent)	10(20%)	21(42%)	3(6%)	19(38%)	

Adverse effects

Burning sensation was reported more in group B with 12 (24%) participants when compared to only 6 (12%) patients in group A. Dryness was noted in 2 (4%) in Group B and only one participant (2%) in Group A. Erythema was observed in 3 (6%) in Group B and only in 1 participant (2%) in Group A. Pruritus was noted in 4 (8%) in Group B and in 3 participants (6%) in Group A. The adverse effects were slightly more frequently observed in Group B when compared to Group A though this is not statistically significant ($P = 0.94$). Side effects were well tolerated by participants in both the Groups

Discussion

Acne is one of the prevalent skin ailments that present to dermatologists in day-to-day practice. Diagnosis of acne is easy; however, treatment selection depends on multiple factors such as grading of acne, duration of disease, previous treatments are taken, and the tendency for scarring and post-inflammatory pigmentation. So, procedure should be tailored to the individual patient, and it must also take into record the influence of acne on patients quality of life. Various treatment choices are available, but there is a necessity for an effective additional treatment to accelerate the improvement in acne vulgaris. Both topical and systemic retinoids are the mainstay in the treatment ladder for acne. Chemical peeling is also gaining importance, especially in mild-to-moderate acne. To the best of our knowledge, there are no published data about comparing 40% MA peel vs. 30% SA in acne treatment. However, few studies were published using either SA or MA alone to treat acne with different concentrations. This prospective study was carried out in 100 patients with mild-to-moderate acne vulgaris.

In our study, females outnumbered males with a male to female ratio of 1:2.1. This finding is consistent with previous studies by Vijay Kumar Garg *et al.*[6] (0.3:1), Doaa S.Sayed *et al.*[11] (0.1:1), Sadaf Fasih *et al.*[12] (0.7:1), and Olga Lekakh *et al.*[13] (0.3:1). However, studies conducted by Dayal S *et al.*[14] and Shishira *et al.*[15] observed a male preponderance of 1.1:1 and 1:0.6, respectively.

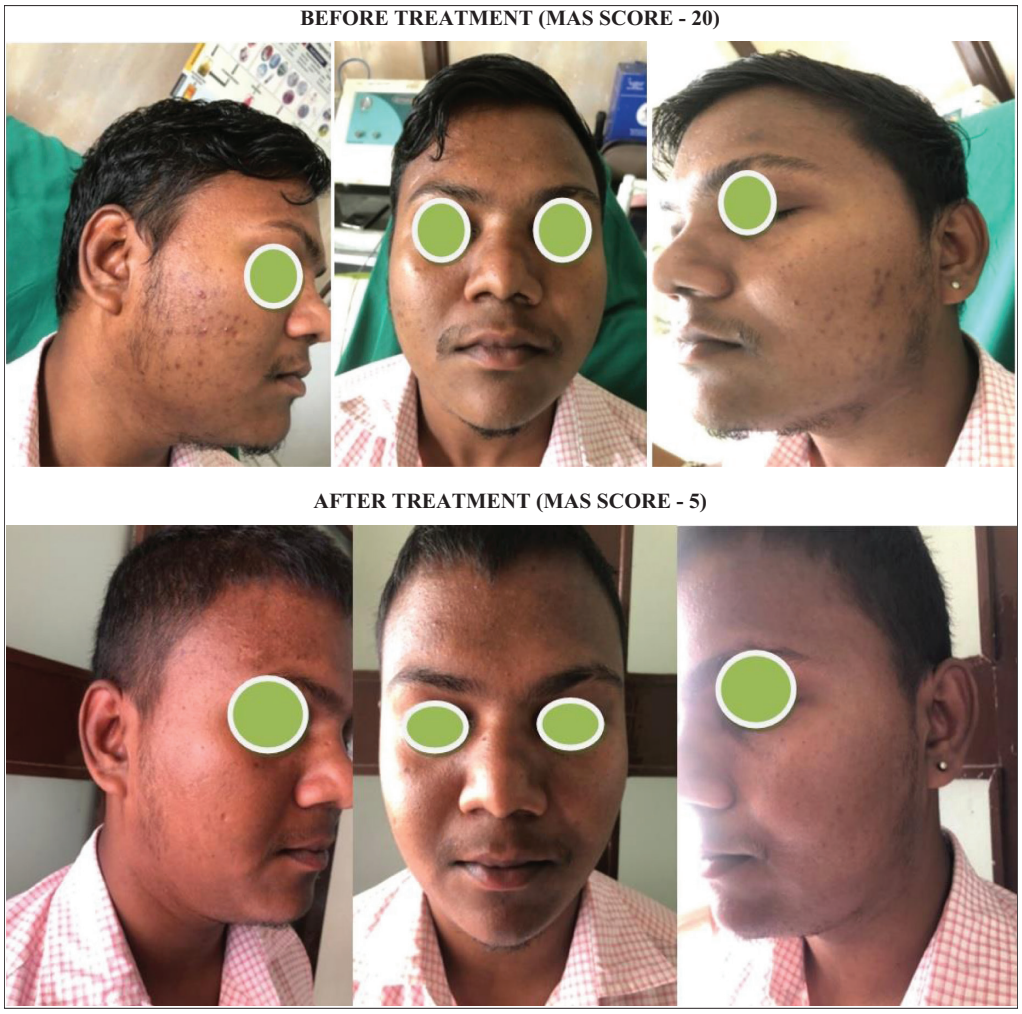

Figure 1: Before and after (12 weeks) treatment photographs of a patient treated with 40% mandelic acid peel (male)—group A. Before treatment (MAS score 20). After treatment (MAS score 5)

Table 4: Showing mean MAS score for both groups

Study groups	Mean Baseline MAS score	MAS score After 12 weeks treatment	*P* Value
Group A	20.16	4.95	0.0001
Group B	22.80	6.64	0.0001

Table 5: Mean percentage improvement between groups A and B

Peeling agent groups	Mean percentage improvement	*P* Value
Group A	75.92 %	0.187
Group B	72.96 %	

Age group and gender ratio

In our study, a maximum number of acne patients belonged to 15 to 25 years in both Group A 72% and Group B 68% making it 70% of the total 100 participants. The mean age of the study population in Group A and Group B was 20.3 and 20.4 years, respectively. This was more or less similar to studies done by Vijay Kumar Garg *et al.*,[6] Jartarkar *et al.*,[16] Shishira *et al.*,[15] and Doaa S.Sayed *et al.*[11] Slightly lesser mean age of 19.54 and 19.21 was noted by Dayal S *et al.*[14] and Sadaf Fasih *et al.*[12] respectively. A mean age of 26.3 was reported by Olga Lekakh *et al.*[13] The higher prevalence of acne in adolescents is a recognized entity, and the present study was consistent with it [Table 6].

Precipitating factors

In our study, 17% of participants mentioned increased acne due to diet, including regular rice and oily food intake; summer exacerbation was seen in 23%, premenstrual flare in 19% and stress-induced exacerbation was noted in 9%. In a study conducted by Salomone *et al.*[17] in Santiago, of the Forty patients between 13 and 25 years of age, 70% saw a flare-up in acne lesions with stress, and 42% saw a worsening with menstrual period, 58% saw a worsening with a variety of foods, especially mayonnaise, butter, dairy, nuts and chocolate.

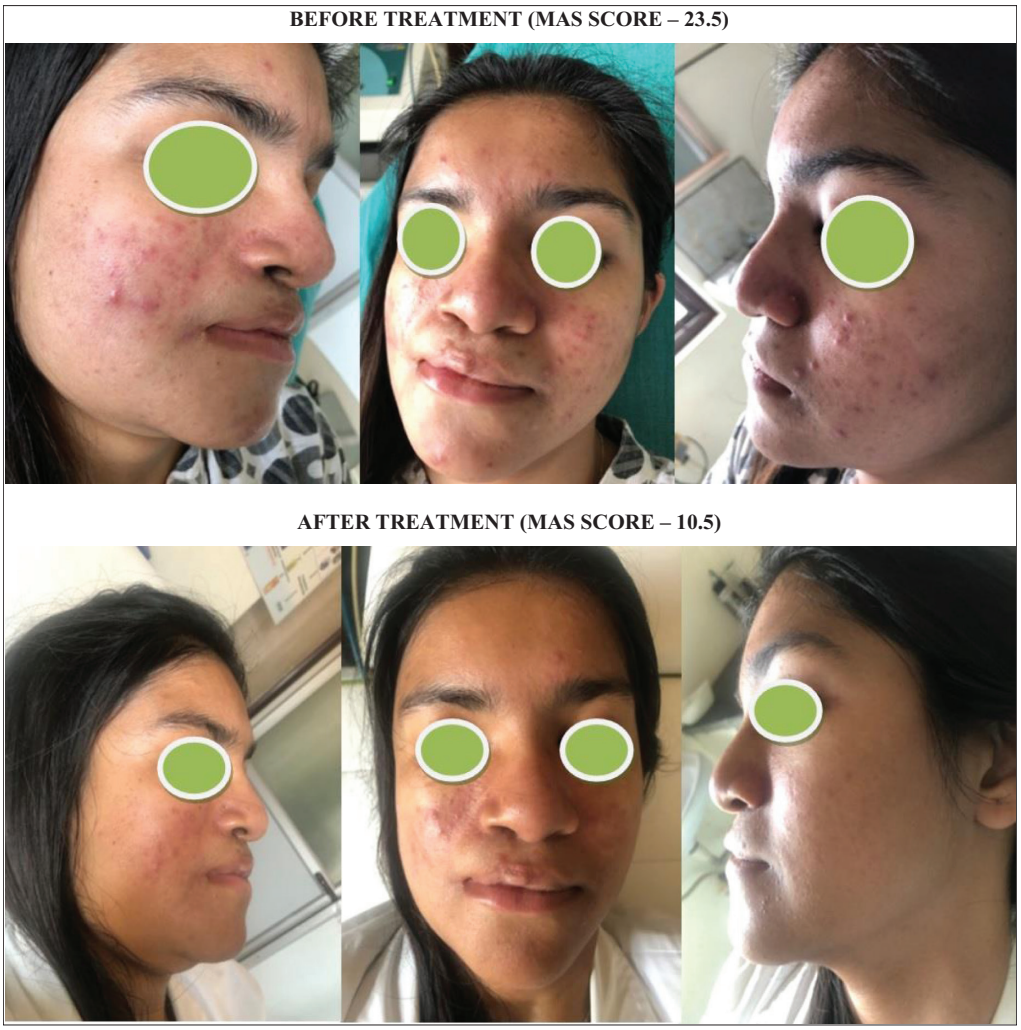

Figure 2: Before and after treatment (12 weeks) photographs of a patient treated with 40% mandelic acid peel (female)—group A. Before treatment (MAS score 23.5). After treatment (MAS score 10.5)

Table 6: Comparative analysis of age and gender ratio from studies done elsewhere

S. no.	Researcher	Peeling agents used	Mean age	Sex preponderance (male:female)
1	Our study	40% mandelic acid vs. 30% salicylic acid peel	20.35	1:2.1
2	Vijay kumar Garg *et al.*[6]	Glycolic acid vs. SMP	22	0.3:1
3	Dayal *et al.*[14]	45% mandelic acid vs. 30% Salicylic acid peel	19.54	1.1:1
4	Jartarkar *et al.*[16]	20% salicylic acid and 30% mandelic acid peel	21.65	1:1.5
5	Shishira *et al.*[15]	30% mandelic acid peel	21.13	1:0.6
6	Doaa S.Sayed *et al.*[11]	SA peel vs. lactic acid peel	24.90	0.1:1
7	Sadaf Fasih *et al.*[12]	SA peel	19.21	0.7:1
8	Olga Lekakh *et al.*[13]	SA peel vs. pulsed dye laser	26.3	0.3:1

Worsening of acne during summer was noted in 23 (23%) participants in our study. Previous studies noted variable results regarding seasonal variation in acne. Sardana *et al.*[18] also reported worsening of acne during summer. The reason for aggravation of acne in summer may be because increased sweating may result in increased growth of the lipophilic Propionibacterium. The association of these factors with acne exacerbation noted in our study was in accordance with previous studies. One Saudi Arabian study by Al Ameer [19] reported worsening of acne in winter and improvement in summer as it was thought that it could be due to the bactericidal effect of ultraviolet light.

Treatment efficacy

In our study with respect to mild acne (Grade I), good improvement was noted in 16% of the participants in Group A (40% MA) and in 12% of the participants in Group B (30% SA). Excellent improvement was noted in 20% of participants in Group A and 6% of participants in

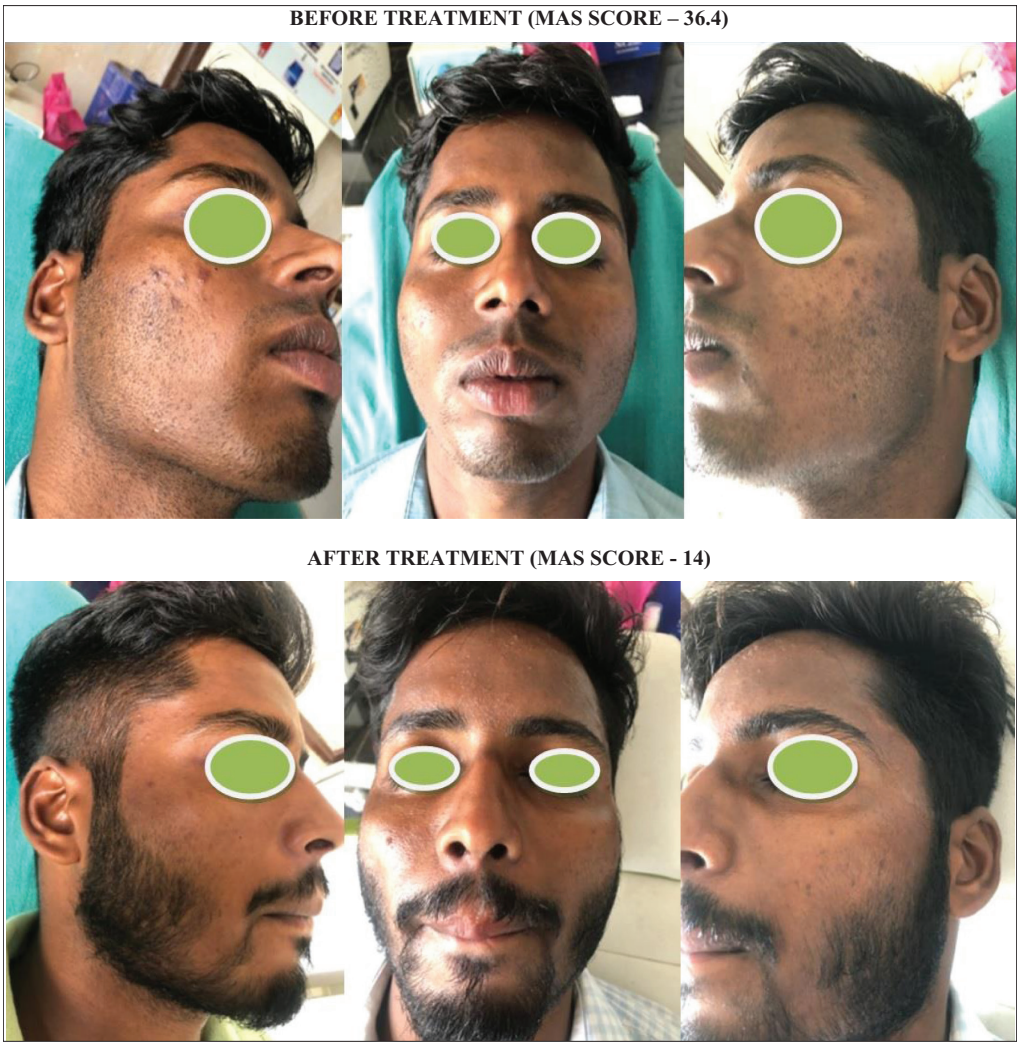

Figure 3: Before and after treatment (12 weeks) photographs of a patient treated with 30% salicylic acid peel (male)—group B. Before treatment (MAS score 36.4). After treatment (MAS score 14)

Group B. With respect to moderate acne (Grade II), good improvement was reported in 18% of the participants in Group A (40% MA) and in 42% of the participants in Group B (30% SA). Excellent improvement was noted in 42% in Group A and 38% participants in Group B.

In our study, the mean MAS score after 12 weeks of treatment improved to 4.95 from a baseline score of 20.16 in Group A and 6.64 from the baseline score of 22.80 in Group B. The improvement in mean MAS score was more or less equal in both the Groups indicating both MA peel and SA peel were equally effective in Grade I and Grade II acne vulgaris. The mean percentage of improvement was 75.92% in Group A and 72.96% in Group B, and the difference was not statistically significant; thus, both the peels were equally efficacious in our study.

Adverse effects

Both peels were tolerated well by the participants in both Groups. The adverse effects were slightly more frequently observed in Group B when compared to Group A though this is not statistically significant ($P = 0.94$). The adverse effects were transient, and they subsided within 24 h. The adverse effects were well tolerated in the study by Dayal *et al.*[14] also.

Conclusion

Both 40% MA peel and 30% SA peel were equal in efficacy in the treatment of Grade I and Grade II acne vulgaris in South Indian patients. Both the peels were well tolerated and safe.

Limitations

In our study no follow-up was done after 12 weeks of treatment to know the long-term efficacy as well as reoccurrence rate of acne vulgaris. Therefore, prospective studies, with more number of participants, and more number of treatment sessions with a long-term follow-up period of at least 6 months to 1 year is needed to substantiate our result.

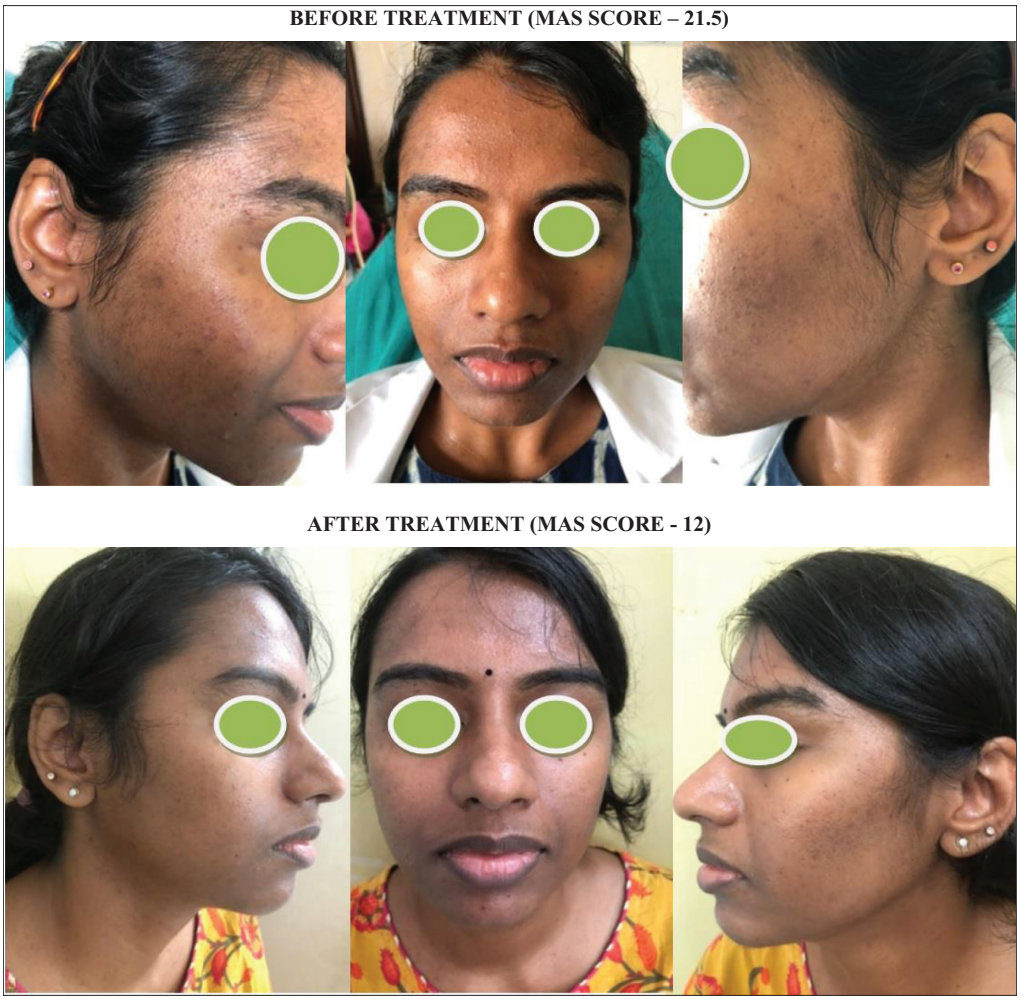

Figure 4: Before and after (12 weeks) treatment photographs of a patient treated with 30% salicylic peel (female)—group B. Before treatment (MAS score21.5). After treatment (MAS score 12)

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

The Relationship of Demodex Density with Acne Severity

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Abstract

Introduction: Demodex (D.) mites play a role in the etiology of many dermatological diseases. **Objectives:** The aim of this study was to reveal the relationship between acne severity (mild, moderate, and severe acne) and Demodex density in patients with acne vulgaris and compare this with the healthy population. **Materials and Methods:** In total 150 patients with acne vulgaris and 60 healthy individuals were evaluated. Patients diagnosed with acne vulgaris were divided into three groups as mild, moderate, and severe. The gender, body mass index, history of diabetes mellitus, smoking, alcohol use, tea and coffee consumption, usage frequency of moisturizer, facial cleanser and concealer, and skin type (dry/sensitive, mixed, and oily) were recorded. Demodex density was measured by using the standard superficial skin biopsy method. **Results:** Demodex infestation was observed in 40 (26.6%) of the acne patients and 13 (21.6%) of the healthy control group. The Demodex infestation was observed in 16 (32%) of the mild acne group, 15 (30%) of the moderate acne group, and 9 (18%) of the severe acne group; there was no significant difference between the control group and severity of acne. In patients with acne, being over 25 years of age 2.6-fold, sensitive-dry skin type 7.4-fold, and obesity 4.06-fold increased risk of Demodex infestation. **Conclusion:** In this study, we did not detect an increased incidence of Demodex, including disease severity, in patients with acne vulgaris. However, we showed that the density of Demodex was increased in those aged 25 years and older, obese patients, and those with sensitive-dry skin in patients with acne.

Keywords: Acne vulgaris, mites, obesity

Introduction

Demodex mites most frequently colonize the eyelids, forehead, nose, nasolabial folds, cheek, and chin.[1] Up to 80–90% of humans may harbor the Demodex organism but rarely causes clinical symptoms.[1,2] However, there are publications in the literature that Demodex mites play a role in the etiology of many dermatological and ocular disorders. Cutaneous diseases of the pilosebaceous unit caused by Demodex mites can be a primary skin disease or an exacerbation of inflammatory dermatoses such as papulopustular rosacea, facial folliculitis, acne vulgaris, and chronic blepharitis.[1,3,4]

Acne vulgaris is a multifactorial disease of the pilosebaceous unit that frequently affects adolescents and young adults.[5] Hyperseborrhea, disseborrhea, altered keratinization of the pilosebaceous duct, *Cutibacterium acnes* (C. acnes), and inflammation play a role in the pathophysiology of acne.[6] Demodex mites can cause perifollicular inflammation via protease and lipase enzymes and can contribute to the development of acne lesions by causing follicle occlusion and secretion of inflammatory cytokines.[7]

In this study, we aimed to reveal the relationship between acne severity (mild, moderate, or severe acne) and Demodex density in patients with acne vulgaris and compare this with the healthy population. In addition, we aimed to reveal the effects of sociodemographic characteristics and diet type on Demodex density.

Materials and Methods

Patients who applied to the outpatient clinic of dermatology and gave consent to participate by filling out a questionnaire were included in the study. In total

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150 patients with acne vulgaris and 60 healthy individuals were evaluated. Patients diagnosed with acne vulgaris were divided into three groups as mild, moderate, and severe according to the Global Acne Severity Scale (GASS), and 50 patients were included in each group.[8]

The gender, body mass index (BMI), history of diabetes mellitus, smoking, alcohol use, tea-coffee consumption (daily or less often), usage frequency of moisturizer, facial cleanser and concealer, and skin type (dry/sensitive, mixed, or oily) were recorded by the questionnaire. If the frequency of application of the facial cleansing product was more than once a day, it was considered as frequent use, moderate use once a day, and infrequent use less than once a day. If the frequency of application of moisturizer and concealer was more than once a day, it was considered as frequent use, moderate use once a day, and infrequent use less than once a day.

Nutritional style (Mediterranean diet, protein-based diet, vegetarian diet, and American-style diet) was also evaluated.

Demodex density is considered as the number of parasites per surface area. Accordingly, the detection of ≥5 Demodex mites in a 1 cm² area is considered as infestation. Demodex density was measured in all patients and controls from the clinically most suspicious area for Demodex using the standard superficial skin biopsy (SSSB) method which is a noninvasive method. In the healthy control group, samples were taken from the areas of the most oily skin (forehead, cheek, chin, etc.). In the SSSB method, the place from where the sample will be taken is cleaned with alcohol and a drop of cyanoacrylate adhesive is applied on the slide, and the adhesive surface of the slide is pressed against the patient's skin for about 1 min. A drop of immersion oil is dripped onto the sample, the coverslip is closed and examined under a microscope with 10× and 40× objectives. With this method, adult, larva, nymph, and egg forms of mites are investigated and the number of Demodex mites seen in a 1 cm² area is recorded.

The inclusion criteria for the study were not to have received topical or oral acne and rosacea treatment in the last six months, to be over 18 years old, and to have consented to participate.

Statistical analysis

The SPSS 23.0 statistical package program was used in the analysis of the data. The descriptive statistics of the evaluation results were given as numbers and percentages for categorical variables, and as mean, standard deviation (sd), minimum (min), and maximum (max) for metric variables. The conformity of the measurement data to the normal distribution was examined with the one-sample Kolmogorov-Smirnov test. In the comparisons of the measurement data of two independent groups, the Student *t*-test was used when the normal distribution condition was met, the Mann-Whitney U-test was used when the normal distribution condition was not met. The chi-square test was used to analyze the differences between the categorical ratios. In addition, factors that may be associated with Demodex infestation in acne patients were evaluated using logistic regression analysis in multivariate analyses. The interactions of the variables with each other were evaluated with the correlation matrix. The enter method was used when the variables were included in the models. The Hosmer-Lemeshow test was used to evaluate the fit of the models, and the Nagelkerke R^2 was used to evaluate the explanatory power. Odds ratio (OR) values were presented with a 95% confidence interval (CI) and the statistical significance level was taken as $P < 0.05$.

Results

A total of 210 people, including 150 patients with acne and 60 control group, were included in our study. The age range of the population was between 18 and 46 years. The mean age was 24.39 ± 6.139. Sociodemographic data of acne and control group are summarized in Table 1.

The Demodex infestation was observed in 40 (26.6%) of the acne patients and 13 (21.6%) of the healthy control group. Although Demodex infestation was more common

Table 1: Sociodemographic data of acne and control group

	Acne *n* = 150	Control *n* = 60	*P*–value
Gender, female, *n* (%)	119 (79.3)	44 (73.3)	0.363
Age, ≥25years, *n* (%)	59 (39.3)	33 (55)	**0.039**
Demodex infestation, *n* (%)	40 (26.6)	13 (21.6)	0.568
Facial cleanser, *n* (%)			0.182
Rare	111 (74)	45 (75)	
Moderate	27 (18)	14 (23.3)	
Frequent	12 (8)	1 (1.6)	
Moisturizer, *n* (%)			0.098
Rare	118 (78.6)	47 (78.3)	
Moderate	16 (10.6)	11 (18.3)	
Frequent	16 (10.6)	2 (3.3)	
Concealer, *n* (%)			0.264
Rare	118 (78.6)	49 (81.6)	
Moderate	21 (14)	10 (16.6)	
Frequent	11 (7.3)	1 (1.6)	
Skin type, *n* (%)			0.072
Dry/sensitive	12 (8)	9 (15)	
Mixed	87 (58)	39 (65)	
Oily	51 (34)	12 (20)	
Smoking , *n* (%)	20 (13.3)	11 (18.3)	0.284
Alcohol consumption, *n* (%)	16 (10.6)	5 (8.3)	0.239
Daily coffee consumption, *n* (%)	55 (36.6)	21 (35)	0.875
Daily tea consumption, *n* (%)	103 (68.6)	40 (66.6)	0.870
Diabetes mellitus, *n* (%)	4 (50)	4 (50)	0.229
Obesity, *n* (%)	13 (8.6)	9 (15)	0.212

in acne patients, the difference was not statistically significant (P = 0.568). The Demodex infestation was observed in 16 (32%) of the mild acne group, 15 (30%) of the moderate acne group, and 9 (18%) of the severe acne group; there was no significant difference between the control group and severity of acne (P = 0.229). Demodex density was also not associated with acne severity.

The Demodex infestation was statistically significantly higher over the age of 25 years when compared to the participants under 25 years old (P = 0.001).

A comparison of the sociodemographic characteristics of acne patients under and over the age of 25 is presented in Table 2.

Demodex positivity was observed in 17 (18.7%) of the acne patients under 25 years old and 23 (39%) of those over 25 years old, and a statistically significant difference was observed (P = 0.008). Of the acne patients under the age of 25, 24 (26.4%) were in the mild acne group, 30 (32.9%) were in the moderate acne group, and 37 (40.6%) were in the severe acne group. Acne severity was statistically significantly higher under the age of 25 (P = 0.029) years.

The comparison of sociodemographic and clinical characteristics of patients with and without Demodex in patients with acne is summarized in Table 3. The Demodex infestation was significantly higher in the sensitive-dry skin type (P = 0.003).

Among the acne patients, 40% of those with Demodex infestation and 20.9% of those without Demodex infestation use facial cleansing products. This rate is statistically significantly higher in acne patients with Demodex (P = 0.043). In addition, no statistically significant difference was observed between the acne groups with and without Demodex in terms of smoking, alcohol use, and, tea and coffee consumption.

There was no significant difference in diet between the control group and the acne group (P = 0.446) and between

Table 2: Comparison of sociodemographic characteristics in acne patients under and above 25 years old

	<25 years n = 91	≥25 years n = 59	P-value
Gender, female, *n* (%)	68 (74.7)	51 (86.4)	0.100
Demodex infestation, *n* (%)	17 (18.7)	23 (39)	**0.008**
Facial cleanser, *n* (%)			0.117
Rare	71 (78)	40 (67.8)	
Moderate	16 (17.6)	11 (18.6)	
Frequent	4 (4.4)	8 (13.6)	
Moisturizer, *n* (%)			0.972
Rare	71 (78)	47 (79.6)	
Moderate	10 (11)	6 (10.2)	
Frequent	10 (11)	6 (10.2)	
Concealer , *n* (%)			0.499
Rare	72 (79.1)	46 (78)	
Moderate	14 (15.4)	7 (11.9)	
Frequent	5 (5.5)	6 (10.1)	
Skin type, *n* (%)			0.124
Dry/sensitive	4 (4.4)	8 (13.5)	
Mixed	54 (59.3)	33 (55.9)	
Oily		18 (30.5)	
Smoking, *n* (%)	16 (17.6)	4 (6.8)	0.081
Alcohol consumption, *n* (%)	11 (12.1)	5 (8.5)	0.595
Daily coffee consumption, *n* (%)	36 (39.6)	19 (32.2)	0.390
Daily tea consumption, *n* (%)	62 (68.1)	41 (69.5)	1.000
Diabetes mellitus, *n* (%)	1 (1)	3 (5.1)	0.300
Obesity, *n* (%)	9 (9.9)	4 (6.8)	0.568
Acne severity, *n* (%)			**0.029**
Mild	24 (26.4)	26 (44.1)	
Moderate	30 (32.9)	20 (33.9)	
Severe	37 (40.6)	13 (22)	

Table 3: The comparison of sociodemographic and clinical characteristics of patients with and without demodex in patients with acne

	Demodex positive (n = = 40)	Demodex negative (n = 110)	P-value
Gender, female, *n* (%)	31 (77.5)	88 (80)	0.820
Age, ≥25 years, *n* (%)	17 (42.5)	74 (67.3)	**0.008**
Smoking, *n* (%)	3 (7.5)	17 (15.5)	0.280
Alcohol consumption, *n* (%)	4 (10)	12 (10.9)	1.000
Daily tea consumption, *n* (%)	29 (72.5)	74 (67.3)	0.691
Daily coffee consumption, *n* (%)	12 (30)	43 (39)	0.343
Facial cleanser, *n* (%)			
Rare	24 (60)	87 (79.1)	**0.043**
Moderate	10 (25)	17 (15.5)	
Frequent	6 (15)	6 (5.4)	
Moisturizer, *n* (%)			0.804
Rare		88 (80)	
Moderate	5 (12.5)	11 (10)	
Frequent	5 (12.5)	11 (10)	
Concealer, *n* (%)			0.319
Rare	29 (72.5)	89 (80.9)	
Moderate	6 (15)	15 (13.6)	
Frequent	5 (12.5)	6 (5.4)	
Skin type, *n* (%)			**0.003**
Dry/sensitive	8 (20)	4 (3.6)	
Mixed	18 (45)	69 (62.7)	
Oily	14 (35)	37 (33.6)	
Acne severity, *n* (%)			0.229
Mild	16 (40)	34 (30.9)	
Moderate	15 (37.5)	35 (31.8)	
Severe	9 (22.5)	41 (37.2)	
Diabetes mellitus, *n* (%)	1 (2.5)	3 (2.7)	1.000
Obesity, *n* (%)	8 (20)	14 (12.7)	0.204

Table 4: Linear regression analysis

	Odds ratio (95% CI)	*P*-value
Age, ≥25 years	2.686 (1.176–6.138)	**0.019**
Gender, female	1.528 (0.574–4.061)	0.396
Skin type, dry/sensitive	7.404 (1.849–29.656)	**0.005**
Skin type, mixed	3.799 (0.885–16.306)	0.072
Acne severity, severe	0.655 (0.223–1.920)	0.440
Acne severity, moderate	0.972 (0.377–2.506)	0.953
Obesity	4.068 (1.130–14.642)	**0.032**

Hosmer Lemeshow Test $P = 0.723$ Nagelkerke R^2:**19%**, Omnibus tests of model *P*: 0.003.

CI = confidence interval

the groups with and without Demodex in patients with acne ($P = 0.312$).

Linear regression analysis was performed to identify possible risk factors for Demodex infestation in acne patients. Linear regression analysis was presented in Table 4. Being over 25 years old, sensitive-dry skin type, and obesity were observed as risk factors for Demodex infestation in acne patients. In patients with acne, being over 25 years of age 2.6-fold, sensitive-dry skin type 7.4-fold, and obesity 4.06-fold increased risk of Demodex infestation.

Discussion

In this study, we found the prevalence of Demodex in acne patients to be 26.6%, similar to healthy volunteers. In addition, we did not find a relationship between acne severity and the presence of Demodex. In literature, Demodex mites have been considered to be possibly related to many kinds of facial dermatoses, such as papulopustular rosacea, facial folliculitis, and chronic blepharitis.[4,7]

Demodex mites specifically penetrate the keratinocytes lining the pilosebaceous follicles and feed on sebum and cellular proteins obtained by protease in salivary enzymes.[7] The enzymatic process, which starts with the lipase enzymes that Demodex uses in the digestion of lipids and microorganisms, may lead to the deterioration of the follicular epithelium and cause perifollicular inflammation.[7] Demodex mites can also cause mechanical blockage of the follicle opening, a granulomatous foreign body reaction, and a host immune response causing inflammatory changes.[7] Although all these suggest that Demodex parasites are involved in the etiopathogenesis of acne, there are different study results in the literature regarding the relationship between acne vulgaris and Demodex.

In two studies comparing the relationship between acne and Demodex in literature; the prevalence of Demodex was reported as 11.8% and 15.38%, these rates were lower compared with our study.[9,10] Contrary to our study, Akçınar *et al.* [11] reported a higher prevalence of Demodex as 42.6% in acne patients, and showed that Demodex positivity could be a risk factor for the development of acne vulgaris.

A meta-analysis by Zhao *et al.*[12] concluded that acne vulgaris was also significantly associated with Demodex infestation, but not as close as in rosacea. Aktaş Karabay *et al*. [7] showed that Demodex infestation rates were higher in patients with rosacea, acne vulgaris, and seborrheic dermatitis than in controls, additionally rates were significantly higher in the rosacea group. On the other hand, Okyay *et al.* [13] showed no significant difference observed between D. folliculorum prevalence and between the group with acne or without acne and between the types of acne as in our study.

Zhao *et al.* [14] concluded that Demodex prevalence increases with age, oily or mixed skin sebaceous hyperplasia appears to favor Demodex proliferation, and Demodex infestation may be associated with acne vulgaris. They reported that age, skin type, and skin disease independently correlate with Demodex infestation. Also, having a Demodex infestation for oily or mixed skin has increased Demodex 2.1-fold more than those for dry or neutral skin. The same study concluded that for oily or combination skin, sebaceous hyperplasia appears to favor Demodex proliferation and Demodex infestation may be associated with acne vulgaris.[14] In our study different from Zhao *et al.* [14], the frequency of Demodex was found to be higher in acne patients with sensitive-dry skin, and having a sensitive-dry skin type was found to be associated with 7.4-fold increased Demodex infestation in patients with acne. We think that additional cosmetic products that can be used in sensitive dry skin types can be a food source for Demodex.

Akçınar *et al*.[11] found that cigarette smoking did not influence the positivity and density of Demodex in the adolescent and postadolescent acne group; alcohol consumption was related to Demodex positivity in the postadolescent acne group, but not in the adolescent acne group.[11] In another study, Okyay *et al*.[13] showed that D. folliculorum was significantly more common in alcohol consumers and was more common in seborrheic skin. Similarly, in our study, the prevalence of Demodex was significantly higher in patients with postadolescent acne, we found being over 25 years of age was associated with 2.6-fold increased Demodex infestation in patients with acne. Also, we found that alcohol and smoking did not influence the positivity of Demodex.

Zhao *et al.*[14] and Dokuyucu *et al.*[15] found that gender was not statistically correlated with Demodex infestation as in our study. Yazısız *et al.*[5] did not found relationship between Demodex positivity and age, gender, number of baths per week, use of make-up materials, and use of shared towels.

We did not find any relation between the use of concealer and moisturizer and Demodex infestation. However, we showed that acne patients with Demodex infestation had a higher frequency of use of facial cleansing products than acne patients without Demodex infestation. This may be due to the search for the treatment of dry skin sensitivity and grating feeling due to Demodex.

In our study; we did not find any correlation in tea-coffee consumption in acne patients when compared with controls and between acne patients with and without Demodex consumption, which are the triggers of rosacea disease, which has been shown to be associated with Demodex infestation in the literature.

Dokuyucu *et al.*[15] reported that Demodex positivity was significantly higher in obese patients. Some authors suggested that poor blood glucose regulation, obesity, and metabolic syndrome all increase the susceptibility to D. folliculorum mite infestation.[11] Although no difference was observed between the acne and control groups in terms of obesity and dietary habits in this study, we concluded that being obese was associated with a 4.06-fold increase in Demodex infestation in patients with acne.

Limitations of the study

The number of participants included in this study is small. Since it is a cross-sectional study, the determination of the products used according to the skin types depends on the patient's definition, and before and after the products used could not be fully evaluated.

Conclusion

In our study, we did not detect an increased incidence of Demodex, including disease severity, in patients with acne vulgaris, however, we showed that the density of Demodex was increased in those aged 25 years and older, obese, and those with sensitive-dry skin in patients with acne. According to the results of our study, we can suggest that patients with acne should be investigated in terms of Demodex in patients with symptoms such as facial sensitivity and dryness. However, studies with larger numbers of patients are needed to refine the evidence value of these results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Author's contribution

Conception or design of the work: AF and LBS; data collection: AF, LBS, and OK; data analysis and interpretation: AF, LBS, and DAA; critical revision of the article: AF, LBS, DAA, and OK. Final approval of the version to be published: AF and LBS.

Data availability statement

The data that support the findings of this study are available from the corresponding author.

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Original Article

Evaluating Knowledge Level about Scabies in Primary Care Physicians during the Scabies Outbreak of Turkey

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Abstract

Background: Scabies is a highly contagious and intensely pruritic disease of the skin. Scabies more commonly affects young children, adolescents, and the elderly. Its prevalence is highest in tropical regions, in low-and-middle-income countries, and in times of war. **Materials and Methods:** The study was conducted among physicians working in primary care health care settings in Ordu, Turkey. We developed a survey of 22 questions. A hard copy of the questionnaire was delivered to the physicians. **Results:** A total of 133 responses were obtained. 71 (53.4%) of the physicians were general practitioners (56.5%) and 62 (46.6%) of them were family physicians. 92 of them were working in clinics and 41 of them were working in emergency departments. The overall knowledge score was 83.2%. 60.2% of the physicians had a total score below median score and 39.8% were above median score. The lowest level of knowledge was associated with pathogen, transmission, and incubation period, and the highest knowledge was about clinical diagnosis. Besides, 86.5% of responders had a knowledge score of ≥75%. Physicians <30 years old had a better knowledge score. **Conclusion:** In conclusion, in our study the knowledge about scabies among primary care physicians was adequate, but most of the physicians reported they had difficulty in treating scabies. It is recommended to arrange training programs, including diagnosing and managing dermatological conditions including scabies for the physicians working in the primary health care services.

Keywords: Education, general practitioners, outbreak, public health, scabies

Background

Scabies is a highly contagious and intensely pruritic disease of the skin which is caused by the obligate human ectoparasitic mite *Sarcoptes scabiei* var. *hominis*.[1,2] Although there is wide variation in its prevalence among geographic regions, scabies affects about 200–300 million people worldwide.[2,3] Its prevalence is highest in tropical regions, in low-and-middle-income countries, and in times of war.[2-4] In high-income countries, outbreaks frequently occur in industrial settings, homeless populations, and in people who live in the crowd (schools, aged care facilities, prisons, and refugee camps), and due to delayed diagnosis.[1,4-6]

Scabies more commonly affects young children, adolescents, and the elderly.[1,3,5] Lack of hygiene, malnutrition, poverty, reduced access to health care, indiscriminate sexual contact, dementia, poor sensory perception, and immunodeficiency are factors that predispose to scabies.[2] Both males and females are affected by scabies.[2]

Skin diseases are highly common and cause a great economic burden. Because of the shortage of dermatologists, primary care physicians commonly evaluate and treat patients with skin diseases. The majority of skin-related visits are done to non-dermatologists.[7] Dermatological problems are the third most common problem among patients admitted to the general practice, and dermatologists are one of the four most commonly referred specialties by general practitioners (GPs).[8]

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World Health Organization added scabies to the list of Neglected Tropical Diseases in 2017. Huge case numbers, disease complications, and treatment and prevention costs make scabies a public health burden.[9]

An increase in the prevalence of scabies has been shown in many studies. Also, authors from Turkey declared that there were extremely high numbers of scabies cases in all distinct parts of the country, defined as scabies outbreaks. Wars and migrations, global warming and climate changes, inappropriate treatment, and not whole family treatment could be reasons for this tremendous increase in scabies.[10,11] Nosocomial outbreaks of scabies were also reported.[12] The authors declared that although the total number of people visiting dermatology outpatient clinics decreased during the COVID-19 pandemic, the percentage of scabies-related visits kept increasing.[13]

Because of this huge increase in the prevalence of scabies and most of the cases attended by primary care physicians, we wanted to evaluate the knowledge level of physicians working in primary care.

Materials and Methods

The study was conducted among physicians working in primary care healthcare settings in Ordu, Turkey. This was an observational cross-sectional study that was conducted between March 2021 and June 2021. Written informed consent was obtained from the physicians after an explanation of the aims of the study by the Declaration of Helsinki. Ethical approval was taken before the study. Family physicians and general practitioners working in emergency departments (EDs) and clinics in the first, secondary, and tertiary healthcare settings are included in the study.

We developed a survey according to clinical practice, current knowledge, and previous studies. The survey was not validated. The hard copy of the questionnaire was delivered to physicians and fulfilled by them. Demographic information about age, profession (family physicians and general practitioners), and information about the workplace (primary, secondary, tertiary, clinics, or EDs) were recorded. In the second part of the questionnaire, knowledge questions including questions about the pathogen, incubation period, way of transmission, clinical presentation, diagnosis, treatment, and management of scabies were included.

The questionnaire was evaluated by two expert dermatologists and necessary changes were made in line with their suggestions. A pilot study was conducted on a sample of 20 physicians. The questionnaire consisted of 13 knowledge questions. Four of the questions were multiple-choice questions with only one correct answer, a total of four points. The rest of the knowledge questions have more than one possible correct answer, including the mode of transmission, clinical presentation, diagnosis, and treatment and one point is given for every correct answer, a total of 21 points. The total test score was 25. The score was then transformed into a 100-point scale for easy interpretation. Additionally, sub-scores were created for different aspects of scabies knowledge: including pathogen, transmission and incubation period (four questions, six points), clinical presentation and diagnosis (five questions, 10 points), and treatment and management (four questions, nine points). Out of 136 physicians who filled out the questionnaire, three physicians were excluded from the study.

The participants were included in the study if they were family physicians and general practitioners and if they voluntarily accepted to join the study. Responders who were not working in primary care and who did not want to join the survey were excluded from the study. The responses were anonymous.

At the time of the study, 450 primary care physicians were working in Ordu. The sample size was calculated using the EPI Info™ 7.2.4.0 software and found 109 for the 95% confidence interval. 136 physicians completed the survey. The response rate was 2.2%. A simple sampling method was used to determine the study population.

Statistical analysis was performed using IBM® SPSS® 25 (SPSS Inc., Chicago, IL) software. Categorical parameters are expressed as numbers and percentages, and continuous parameters are expressed as mean and standard deviation. Data distribution was assessed using the Kolmogorov–Smirnov/Shapiro–Wilk tests. For continuous variables, the Mann–Whitney *U* test was used. Pearson's χ^2 or Fisher's Exact χ^2 test was used in the analysis of categorical variables. The Pearson correlation test was used to examine the relationship between scale scores. A *P*-value of <0.05 was accepted as statistically significant, and the confidence interval was 95%.

Sociodemographic and professional characteristics were compared between physicians with low and high knowledge levels (≤ median and > median overall knowledge score, respectively). To detect factors independently associated with high knowledge level, multivariate logistic regression analysis models were done after adjusting for the variables that were significantly associated (*P*-value up to 0.010) with knowledge level in univariate analysis.

Results

A total of 133 responses were obtained. Characteristics of the study population are shown in Table 1. 12 (9%) of the responders were residents in either ED or family medicine departments. The majority of responders (82.7%) faced more than 10 scabies cases in 1 year. The ratio of physicians who had reported difficulty with the diagnosis and treatment of scabies was 16.5% and 27.8%, respectively. According to the majority of the responders,

the prevalence of scabies was increased, and it was more commonly resistant to current treatments.

Answers to the questions were summarized in Table 2. The questions including scabies transmission via close contact and contaminated clothes were correctly answered by all the responders. Only one responder did not know the tunnels were the specific lesion of scabies. All but two of the participants knew that scabies is characterized by intense itching that is worse at night. 61.7% declared that the back is one of the typical areas of scabies infestation. Only 27.8% of the responders knew all the drugs used for the treatment. Antibacterials and antifungals were the wrong choices selected by the responders.

The least commonly truly answered question was about treatment. Although the participants knew the agents used in the treatment of scabies, they thought antimicrobials were also used in the treatment of scabies. Another issue that is not well known about scabies is the body area that scabies mites preferentially infest. Although the participants answered correctly that scabies affects the genital area, breast, and plantar area, they thought that the back area is also among the most frequently affected areas. More than two-thirds of physicians did not know the incubation period of scabies mites correctly.

The question that was left the most blank was the one about Norwegian scabies. One-third of physicians did not answer this question. Two-thirds of the rest had answered this question incorrectly.

As shown in Figure 1, the overall knowledge score was 83.2%. 60.2% of physicians had a total score below the median score and 39.8% were above the median score. The lowest level of knowledge was associated with the pathogen, transmission and incubation period and the highest knowledge was about the clinical diagnosis. Besides, 86.5% of responders had a knowledge score of ≥75%.

Univariate and multivariate logistic regression analysis factors affecting better knowledge level were shown in Table 3. In a univariate logistic regression analysis, physicians less than 30 years old and physicians working as residents had better knowledge scores (P = 0.010 and P = 0.042, respectively). Working as a family doctor or general practitioner and working in the polyclinic or

Table 1: Demographics and professional characteristics of the study physicians by knowledge group

Variables	Subgroups	Median score		P
		≤84 (n = 80)	>84 (n = 53)	
Age				
	<30	27	30	0.023
	30–50	44	17	
	>50	9	6	
Profession				
	General practitioner	42	28	0,105
	Family medicine	34	17	
	Resident	4	8	
Department				
	Polyclinic	57	35	0,524
	Emergency	23	18	
Number of Skabiez cases				
	Number of cases <10	15	8	0,585
	Number of cases ≥10	65	45	
Difficulty in diagnosis				
	Yes	13	9	0,912
	No	67	44	
Treatment resistant scabies				
	Yes	22	15	0,967
	No	17	12	
	Sometimes	41	26	
Increase in the prevalence of scabies				
	Yes	66	42	0,638
	No	14	11	
Treatment resistant scabies				
	Yes	58	43	0,254
	Sometimes	22	10	
Source of information about scabies				
	Journals	11	5	0,439
	Web sites	7	8	
	Medical education	62	40	

Pearson's χ^2 test was used and $P < 0.05$ was considered significant

Table 2: Ratio of information answers given by the responders

	Number (%)
Pathogenic cause of scabies	128 (96.2)
Mode of transmission	
Direct contact	133 (100)
Contaminated clothes	133 (100)
Sexual contact	90 (67.7)
Scabies from animals	
Yes	96 (72.2)
No	37 (27.8)
Incubation period	39 (29.3)
Pruritus at night as classical symptom	131 (98.5)
Tunnels as specific lesion	132 (99.2)
Norwegian scabies	
Correct	28 (21.1)
False	62 (46.6)
Don't know	43 (32.3)
Typical body area	48 (36.1)
Diagnosis	104 (78.2)
Treatment	
Permetrin (topical)	122 (91.7)
Topical sulphure	123 (92.5)
Topical benzyl benzoat	111 (83.5)
Oral ivermectin	68 (51.1)
Treatment of asymptomatic close contact	112 (84.2)
Whole body treatment	110 (82.7)
Repetition of treatment in 7–10 days	126 (94.7)
Washing at 60°C	127 (95.5)
Keeping in a plastic bag for 3 days	118 (88.7)

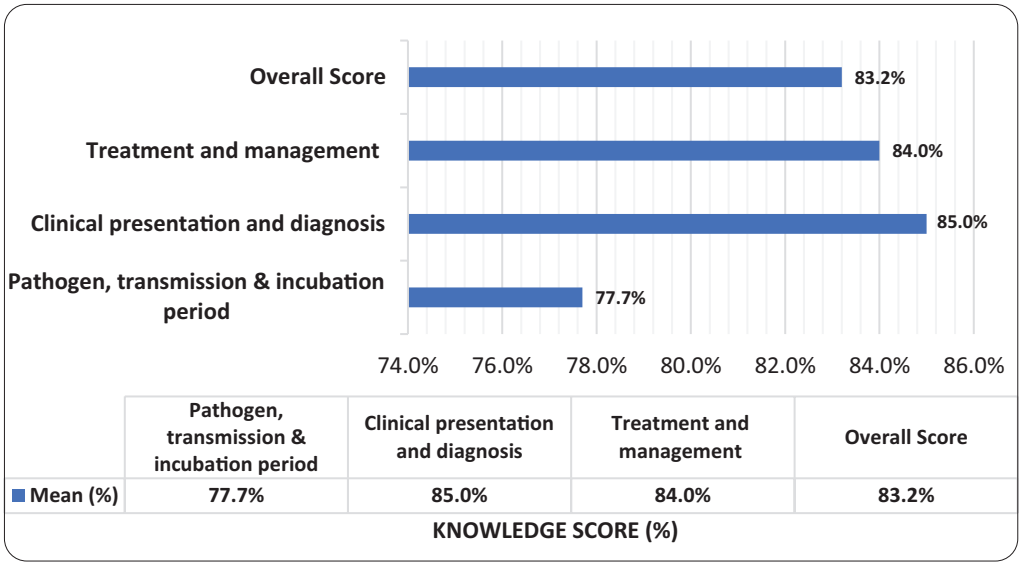

Figure 1: Mean knowledge scores of total and subgroups

Table 3: Univariate and multivariate logistic regression analysis of potential predictors for better knowledge

Variables	Knowledge score median (>84)			
	Univariate		Multivariate	
	P value	Odds ratio [95% min–max]	*P* value	Odds ratio [95% min–max]
Age (<30)	0.010	2.6 [1.25–5.24]	0.029	0.4 [0.20–0.80]
Profession (resident)	0.042	4 [1.1–15.2]	0.098	–
Clinical department (polyclinic vs. ED)	0.524	0.78 [0.37–1.91]	1.000	–
Number of cases (≥10)	0.586	1.3 [0.51–3.3]	0.197	–
Difficulty in diagnosis (No)	0.912	0.95 [0.37–2.40]	0.757	–
Difficulty in treatment (No)	0.862	0.93 [0.41–2.11]	0.819	–
Increased prevalence (Yes)	0.638	1.24 [0.5–3.0]	0.189	–
Treatment-resistant scabies (Yes)	0.257	0.61 [0.26–1.43]	0.046	2.60 [6.60–1.02]
Source of 15 information (medical education vs. others)	0.787	0.93 [0.4–2.0]	0.356	–

It was analyzed enter methods by using logistic regression and $P < 0.05$ was considered significant

GP: General Practitioner

ED: Emergency Department

SD: Standard Deviation

EDs, physicians who encountered <10 or more cases of scabies did not make a statistically significant difference in the total knowledge score and all subgroup scores ($P > 0.05$). In multivariate models adjusted for age, profession, working area, the number of scabies cases per year, difficulty in diagnosis or treatment, increased scabies and increased treatment-resistant scabies, and sources of information about scabies were reviewed and younger physicians dealing with treatment-resistant scabies were found to be associated with better knowledge level.

Discussion

Patients with dermatological diseases account for nearly 5–8% of patients admitted to the ED. In a study conducted in Taiwan, 82% of the inward patients who were diagnosed with scabies visited ED, of which 65% were misdiagnosed. Overcrowding in the ED and scabies in atypical forms were one of the reasons for missed diagnoses.[14] In this current study, the total scores of 43.9% of the physicians working in the ED were above the median score, which is slightly higher than physicians working in the clinics (38.0%) ($P < 0.05$). In another study from the United States, authors analyzed ED visits due to scabies. The average annual expenditure on scabies ED visits was high.[15] In another study from Germany, researchers found that scabies was among the most common dermatological conditions presented to the emergency dermatological unit.[16]

Scabies has an incubation period of 2–6 weeks. In the case of reinfestation within 6 months of the first infection, symptoms may develop in hours to days due to immune memory.[1-5] In our study, less than one-third of physicians

correctly answered the question about the incubation period. In another study, the rate of those who answered this question correctly was 44.5%.[17]

Whether scabies is transmitted from animals is a controversial issue. Scabies can affect over 104 mammal species, including some domestic and wild animals, but these species of mites are different from mites infesting humans. These mites may result in temporary eruptions in humans other than scabies.[3,18] On the contrary, it has also been argued that scabies can also be transferred from animals.[5] In our study, 72.7% of the physicians reported that scabies can transmit from animals, and the ratio was 47.7% in another study.[17]

The main method of transmission is via close skin-to-skin contact. Mites transmission can also occur from textiles or clothing.[1-5] In our study, all the physicians correctly answered questions about transmission via close contact and from infected clothes. In the study from Riyadh, the ratio of correct answers about transmission via close contact and transmission from clothes and linens were 96.8% and 82.4%, respectively.[17] Sexual transmission is another important mode of transmission, so scabies affected as a sexually transmitted disease.[2,4,5] In our study, nearly one-third, and in another study, 44.0% of the responders did not accept scabies as a sexually transmitted disease.[17]

Characteristic history (severe pruritus which increases at night), and typical lesions (burrows, serpiginous tunnels that are formed in the epidermis by the movement of the female mite) on the predilection site aid in the diagnosis.[1-5] In this current study, it was found that nearly all the physicians answered correctly to the questions about the characteristic history and typical lesions of scabies, similar to the previously studied.[17] Pruritus in the family, and friends help in the diagnosis.[3] In the study from Pakistan, 39% of the physicians correctly answered the question regarding itch and the involvement of other family members in the diagnosis of scabies.[19] Although no laboratory test can be used to diagnose scabies, in our study one-fifth of the responders thought that blood tests may aid in the diagnosis of scabies.[3,5]

Pruritus is not mediated by histaminergic mechanisms.[6] Sometimes pruritus may become chronic despite treatment.[1] Severe itching may result in insomnia and affect the quality of life adversely, besides resulting in decreased concentration and nonattendance to school and work.[1-5] Scabies can also cause a feeling of shame, stigmatization, social exclusion, embarrassment, and depression.[2,5] Patients who are taking immunosuppressive and anti-inflammatory agents, individuals treated with topical corticosteroid drugs, and in the infant sense of pruritus may be absent.[6]

Body parts with higher temperatures and a thin stratum corneum are preferred by the scabies mite that include interdigital webs and lateral aspects of the fingers (hands and feet), the volar surface of the forearm, axillary and periumbilical areas, penis and perianal skin, extensor surfaces of elbows and knees, lateral and posterior parts of the feet, buttocks, groin, thighs, penis in men, and areola in women.[1,2,6] In our study, only 36.1% of the responders correctly answered the question about predilection sites of scabies. On the contrary, 61.7% of the responders thought that classical scabies commonly affects the back region.

Crusted (Norwegian) Scabies are characterized by generalized hyperkeratotic lesions. The head, neck, and extremities are mostly located in the body parts. Sometimes it presents as erythroderma. Itching is usually absent or minimal. Crusted scabies is generally seen in immunodeficient individuals. It should be differentiated from psoriasis, eczema, and seborrheic dermatitis.[2,4,6] In our study, only one-fifth of the physicians responded correctly to the question about Norwegian scabies in this current study. In another study, Norwegian scabies was confused with other dermatological diseases.[20]

Permethrin, benzyl benzoate, sulfur-containing compounds, and crotamiton are the topical agents, and ivermectin as a systemic agent is used to treat scabies.[1,2,5] In our study, the majority of physicians correctly knew the agents used in the treatment of scabies. In their study, the authors found that 95.8% of physicians knew that permethrin cream (5%) was used for the treatment of uncomplicated cases,[17] To successfully treat scabies, all household members and close contacts, even asymptomatic, should be treated at the same time. If the household is left untreated, reinfestations may occur.[4,5] In this study, the majority of the responders knew that asymptomatic individuals should also be treated similarly to previous studies.[17] In a study from France, 77% of GPs reported that they treated all household members and any sexual contacts.[21]

In our study, 86.5% of physicians had a knowledge score of ≥75%, which is quite more than the previous studies conducted in Riyadh and Pakistan, 17.1% and 36%, respectively.[17,19]

In a study in Pakistan, it was shown that most of the physicians did not have adequate knowledge about the causative agent, diagnosis, and health education for patients and family members. Fortunately, they were familiar with the transmission, clinical findings, and treatment of scabies.[19]

Outside the human body, at room temperature, mites can survive up to 24–36 h. In colder conditions, this duration increases.[2-4] In our study, 95.5% of the responders knew that clothes should be washed above 60°C, and 88.7% correctly knew that stuff that cannot be washed at the

proper temperature should be kept in plastic bags for at least 3 days, similar to previous studies.[17]

Signs and symptoms may last up to 6 weeks. Pruritus that persists after successful treatment can be managed with emollient antihistamines and topical steroids. Appropriate application of drugs should be encouraged. Face and scalp should not be forgotten in children, the elderly, and in treatment-resistant cases.[4] 82.7% of the responders correctly knew that topical agents should be applied to the whole body instead of applying only the itchy body area.

In our study, younger age and working as a resident were found to be associated with better knowledge scores. In contrast to our findings, authors reported better knowledge scores in older age physicians, physicians with higher education, and physicians who had less time since the last information about scabies was reviewed.[17] In another study from Pakistan, the authors failed to show an association between better knowledge level and increased age or increased experience. Resultantly, they underlined the necessity of continuous medical education for physicians working in primary care.[19]

Skin conditions accounted for 8%–10% of all visits to family physicians in 2002–2005.[21,22] In a study from Australia, authors aimed to assess the differences in diagnostic accuracy between dermatologists and GPs, and they found out that GPs were weak in the diagnosis of scabies, urticaria, pityriasis Versicolor, pityriasis rosea, granuloma annulare, and skin tumors.[23]

Previous data indicate that the majority of patients with skin disease are diagnosed by physicians other than a dermatologist. While preparing a dermatology curriculum for non-dermatologists, it is logical to give importance to the dermatological diseases that are most probably encountered by them and also should include serious skin diseases.[7] Primary care physicians should be trained to focus on the most common dermatological conditions seen in that area.[24]

Since physicians working in the ED and family medicine clinics face a huge number of scabies cases, continuous medical education programs should be encouraged to improve knowledge about scabies. Also, the education of these physicians will result in a reduction in scabies-related healthcare burden.

The first limitation of this study was that its cross-sectional design did not enable us to create a cause-effect relationship. The second limitation was the small sample size. Although primary care physicians from different parts of the health care centers were included in the study, a third limitation can be considered, as the results cannot be generalized to all primary care physicians because of the simple sampling method. We do not know the physicians who did not respond to the survey. They may have a low level of knowledge about scabies. This fact can be added to the limitations of the study.

In this study, the physicians were questioned about transmission incubation period, clinical presentation and diagnosis (specific lesions and symptoms of scabies, mostly affected body parts), drugs used to treat scabies, and procedures that should be done during the treatment. But the factors causing difficulties in diagnosis and treatment were not further questioned. Physicians should be further questioned about if they were able to use any instrument for the diagnosis of scabies, whether they have enough time to examine the patient, difficulty in treatment was patient-related or physician-based, for instance, due to the ineffectiveness of the prescribed drug or the improper use of the drug. Further studies should be done to investigate factors regarding the difficulty in the treatment of scabies.

To our best knowledge, this is the first study evaluating scabies knowledge among primary care physicians in Turkey. In conclusion, in our study, the knowledge about scabies among primary care physicians was adequate, but most of the physicians reported they had difficulty with treating scabies. It is recommended to arrange training programs including diagnosing and managing dermatological conditions, including scabies, for physicians working in primary health care services.

Conclusion

Skin diseases are commonly evaluated and treated by primary care physicians because of a shortage of dermatologists. With huge case numbers, scabies is one of the most commonly encountered dermatological diseases in primary care settings, including the ED. For this reason, continuous medical education programs should be encouraged for physicians working in the ED and family medicine clinics, to better management of scabies cases and reduce scabies-related healthcare burden.

Author's contribution

Concept: FE, Design: FE, SÖ, Definition of intellectual content: FE, SÖ, literature search FE, SÖ, clinical studies:FE, SÖ, experimental studies: FE, SÖ, data acquisition FE,, data analysis: FE,, statistical analysis FE, manuscript preparation FE, manuscript editing: FE, SÖ, and manuscript review: FE, SÖ. All authors contributed to the development of the research protocol, reviewed the manuscript and approved the final version. All authors have seen and approved the manuscript, contributed significantly to the work. The manuscript has not been previously published nor is not being considered for publication elsewhere.

Ethical approval and consent to participate

Written informed consent was obtained from the physicians after explanation of the aims of the study in accordance with the Declaration of Helsinki. Ethical approval was taken prior to the study.

Ethics committee approval

The study was approved by the Ordu University Ethics Committee Chair (approval number: 41).

Availability of data and materials

The data used in this study are available, if necessary, please contact corresponding author (FE).

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Retrospective Analysis of Treatment of Cutaneous Warts with Measles, Mumps, and Rubella Immunotherapy Over 8 Years

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Abstract

Introduction: Warts are benign lesions caused by human papilloma virus. Various types of cutaneous warts include verruca vulgaris, genital warts, and palmoplantar warts. Various therapeutic modalities are available for warts with varying response. These include destructive therapies, cytotoxic agents (Bleomycin), and immunotherapy (measles, mumps, and rubella [MMR], candida antigen, etc.). We have analyzed the efficacy of intralesional MMR immunotherapy in patients with different kinds of cutaneous warts. **Aim:** The purpose of this study was to retrospectively analyze the effectiveness and safety of MMR immunotherapy in the treatment of different kinds of cutaneous warts. **Materials and Methods:** We included all the patients with cutaneous warts receiving MMR vaccine between March 2014 and March 2022. Demographic data were recorded. MMR vaccine was given for four doses at 3 weeks interval or till there was complete clearance, whichever was earlier. Clearance and reduction of wart sizes and potential side effects were recorded. **Results:** A total of 184 patients were enrolled, and 45% patients were women. Predominant age group of patients was 21–40 years. Most common types of warts observed was palmoplantar warts. Complete resolution was seen in 66% patients and partial response in 22% patients. Palmo-plantar and warts on extremities responded completely to immunotherapy, whereas 43% of genital warts had no improvement. Pain at injection site was observed in all patients, and 32% patients had flu-like symptoms. **Conclusions:** Immunotherapy with MMR vaccine shows a promising response in the treatment of palmo-plantar warts and warts on extremities, without any serious adverse effect, whereas the genital warts and verruca plana respond variably to immunotherapy.

Keywords: Cutaneous warts, immunotherapy, MMR, verruca, verruca plana, verruca vulgaris

New Learning Points

1. Immunotherapy with intralesional MMR vaccine is a safe and effective mode of therapy for cutaneous warts over palmo-plantar aspects and the extremities.
2. Genital warts respond poorly to the immunotherapy.

Introduction

Cutaneous warts occur commonly in children and young adults and are more common among certain occupations such as handlers of meat, poultry, and fish.[1] Human papillomaviruses (HPV) infect epithelial tissues of skin and mucous membranes and manifest as warts.[2] There are over 150 distinct HPV subtypes; some tend to infect specific body sites and produce characteristic proliferative lesions at those sites. Spontaneous remission of warts occurs in up to two-thirds of patients within 2 years.[3] In patients with intact cellular immunity, warts tend to regress without therapy; however, recurrence is common.[4] Current therapies for HPV are not virus-specific. Some treatments work by enhancing innate immunity or by local chemotherapeutic effect, and some by tissue destruction, with the goal of destroying the virus-containing epidermis and preserving as much uninvolved tissue as possible. Many researchers have recently shown that cell-mediated immunity affects virus

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multiplication in the wart. As a result, contact sensitizers, imiquimod, intralesional interferons, and oral drugs such as cimetidine have been used as immunotherapies. Little success has been demonstrated with the use of intralesional injections of vaccines and organic antigens. Antigens like *Candida albicans*, trichophyton, measles, mumps, and rubella (MMR), and tuberculin antigens such as purified protein derivative and Bacillus Calmette-Guerin have been injected intralesionally with varied results.[4] This study is aimed at studying the therapeutic effect of MMR vaccine in patients with different types of cutaneous warts.

Materials and Methods

Study design and sampling

In this observational study, we enrolled all the patients who visited the outpatient department in the Department of Dermatology, in a tertiary care hospital in North India from March 2014 to March 2022. We included all the patients diagnosed with warts by two independent dermatologists and treated with MMR immunotherapy (Tresivac). All the demographic data were recorded before starting the treatment. We excluded all the patients with a past history of allergic reaction to MMR vaccine, those on immunosuppressive therapy, pregnant or lactating women, children less than 12 years age, patients with active tuberculosis, and past history of seizures. Patients' demographic and clinical information was obtained from the hospital medical records. Patients were explained the purpose of the study and an informed written consent was obtained from them. Those refusing to consent for the study were excluded from the study and their management was not affected in any way.

Treatment protocol

For treating warts with MMR immunotherapy, the patients received 0.5 mL of reconstituted MMR vaccine into the same single wart, or maximum five large warts in the cases of multiple warts, at 3 weeks intervals until complete response was obtained or for a maximum of four doses. The response of treatment was assessed by a decrease in wart size or number and by a photographic comparison. For this study, complete response was considered if there was complete clearance of the warts, partial if the warts reduced in size by 50%–99%, and no response if there was 0%–49% decrease in wart size. Immediate and late adverse effects of MMR vaccine were also noted for each patient after the treatment session. All the patients were followed up monthly for 6 months to detect any recurrence of warts.

Data collection and data analysis

Approval of the institutional ethics committee was taken before starting the study. Data were entered, checked for completeness, and analyzed using Statistical Package for the Social Sciences (SPSS) software version 23 (Windows, Version 19 Armonk, NY: IBM Corp). Data were expressed as number and percentage for qualitative variables and mean and standard deviation for quantitative variables. Associations between clinical response and patient related variables were established using the χ^2 test. All the results were considered to be significant at the 5% critical level.

Results

During the study period, a total of 184 patients were included in the study. Table 1 describes the distribution of patients according to their baseline characteristics. Approximately half of the patients were from 21 to 40 years age group and 45% of all patients were women. The most common site of warts was palmo-plantar (29%), followed by extremities (26%) and face and neck (22%). Majority of the patients had single warts (48%), whereas approximately one in four patients had more than 10 warts [Table 1]. Four injections were given in 58% of the patients. Complete resolution of symptoms was observed in 66% of the patients, partial response in 22%, and no response or worsening was observed in 12% of the patients [Figures 1–4] On analyzing the clinical

Table 1: Distribution of patients according to their baseline characteristics

Variable	*n* (%)
Age distribution of the patients	
≤20 years	48 (26%)
21–40 years	94 (51%)
41–60 years	34 (19%)
>60 years	08 (04%)
Gender distribution of the patients	
Female	83 (45%)
Male	101 (55%)
Site of warts	
Extremities	48 (26%)
Palmo-planter	54 (29%)
Face and neck	41 (22%)
Genitals	28 (15%)
Periungal	08 (04%)
Scalp	05 (03%)
Number of warts	
Single	89 (48%)
2–5	42 (23%)
6–10	10 (05%)
>10	43 (24%)
Number of injections given	
1	22 (12%)
2	37 (20%)
3	18 (10%)
4	107 (58%)
Clinical response	
Complete	122 (66%)
Partial	41 (22%)
No response/worsening	21 (12%)

response in association with patient-related variables, age group 21–40 years was found to be significantly associated with complete clinical response (P = 0.03) [Table 2]. Furthermore, warts situated on palmo-plantar surfaces and extremities were also significantly associated with complete clinical resolution of symptoms (P = 0.01), whereas 43% (12/28) of the warts situated on genitals had no clinical response or worsening. Gender of the patients or number of warts was not significantly associated with the clinical response of the treatment given. Pain at injection site was reported by all the patients, whereas flu-like symptoms were reported by 32% of the patients.

Discussion

Warts are the exophytic hyperkeratotic papules or plaques caused by the HPV. Spontaneous resolution maybe observed in a few warts; however, as the warts proliferate in the keratinized epithelium, lack of local immunity makes it difficult for spontaneous resolution.[5] The MMR vaccine has been used as an intralesional injection to treat

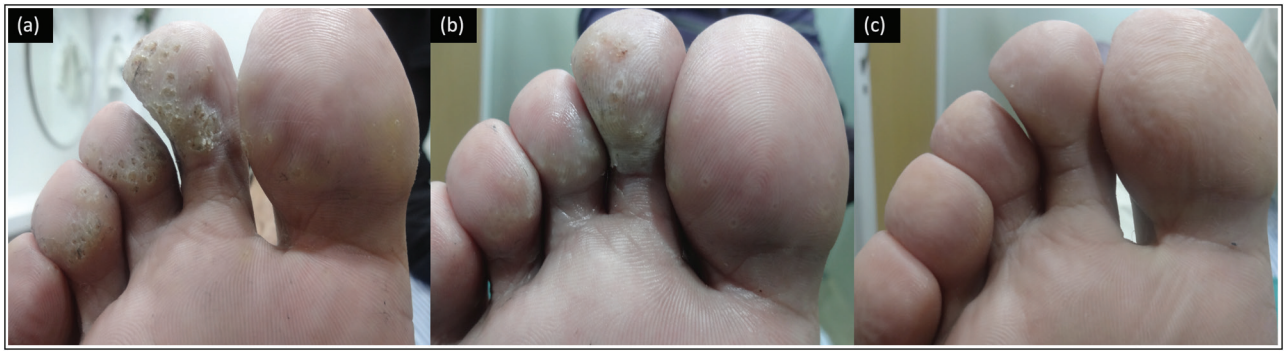

Figure 1: Plantar warts. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing complete response

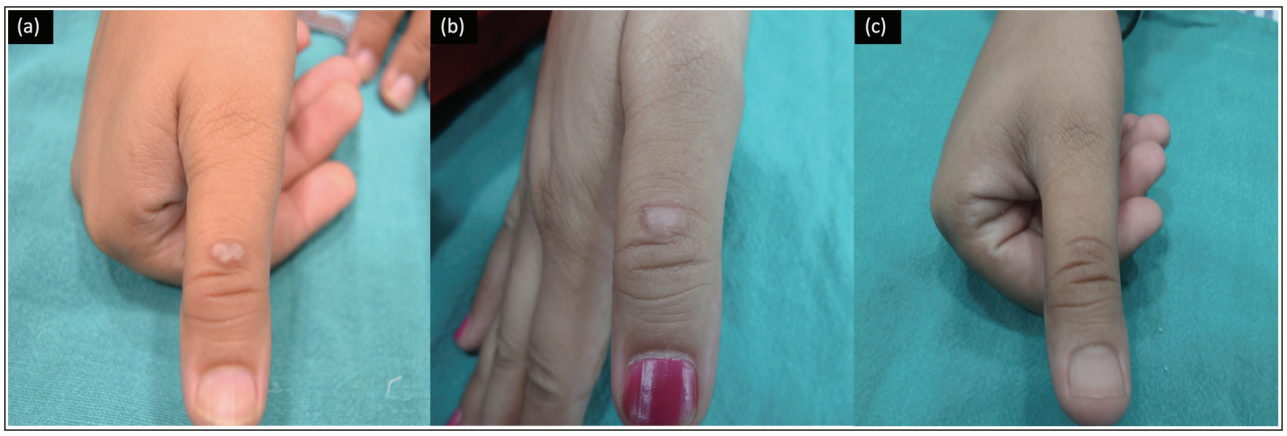

Figure 2: Verruca vulgaris. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing complete response

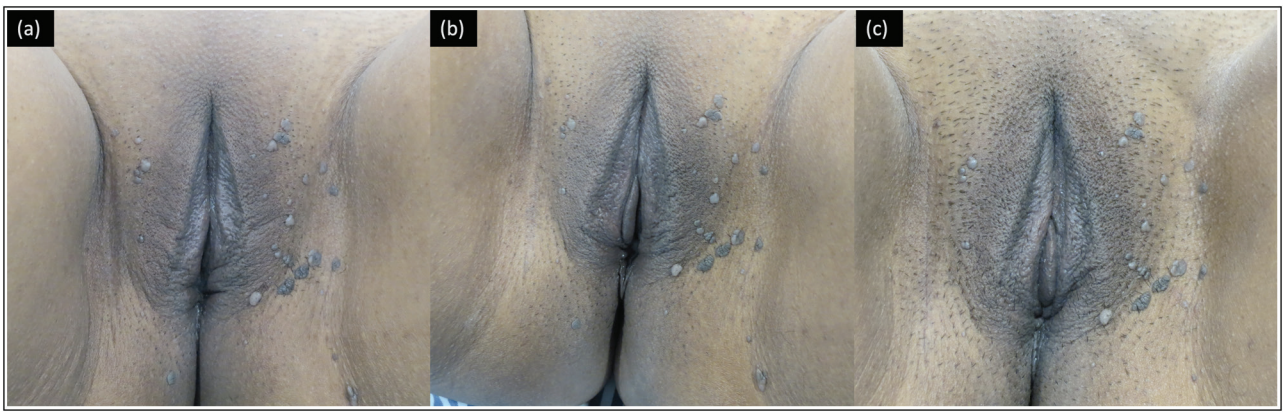

Figure 3: Genital warts. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing no response

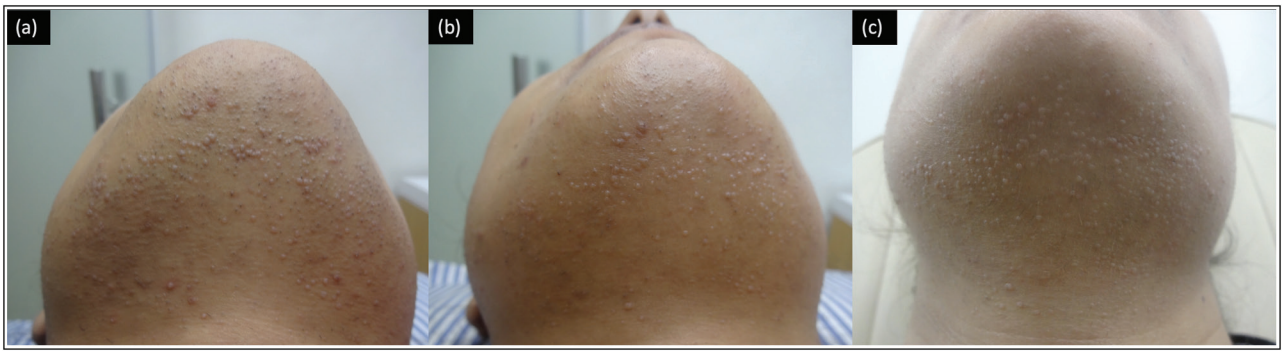

Figure 4: Verruca plana. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing worsening of warts

Table 2: Association of clinical response with patients' demographic and clinical variables

	Clinical response			*P* value
	Complete (n = 122)	Partial (n = 41)	No response/worsening (n = 21)	
Age of the patients				
≤20 years	30	12	2	0.03
21–40 years	76	17	8	
41–60 years	15	10	7	
>60 years	1	2	4	
Gender of the patients				
Female	54	16	14	0.41
Male	68	24	8	
Site of warts				
Extremities	38	8	2	0.01
Palmo-planter	44	8	2	
Face and neck	20	15	6	
Genitals	12	4	12	
Periungal	4	4	0	
Scalp	4	1	0	
Number of warts				
0–5	92	24	12	0.22
6–10	39	16	10	

cutaneous warts by stimulating nonspecific host immune response against HPV antigen by releasing IL-2, 4, 5, 8, 12, IFN-γ, and TNF-α.[6]

The present study observed the patients diagnosed with cutaneous warts and treated with MMR vaccine. A maximum of four treatment sessions were done at our clinic and the clinical response was assessed by the decreasing size of warts. Complete clinical response was observed in 66% of the patients, and it was significantly higher in younger patients and in those with warts situated on palmo-plantar surfaces and extremities. A double-blinded, randomized placebo-controlled trial by Zamanian *et al*.[4] found complete clinical response in 75% of the patients treated with MMR vaccine, with 29% reporting flu-like symptoms. In another randomized trial with similar methodology, Nofal and Nofal[7] studied 110 patients diagnosed with cutaneous warts and found complete clinical response in 81% of the patients and partial response in 10%. Unlike the present study, the authors determined the dose of MMR vaccine according to the extent of intradermal reaction. This method of dose calculation was described by Johnson *et al*.[8] Later, Nofal *et al*.[9] conducted an open label study of 65 patients using standard 0.3 mL dose of MMR vaccine and found that 63% of the patients had a complete response and 23% had a partial response. Furthermore, in the present study, one patient had a relapse at a different site within 6 months and two patients had relapse after 1 year. Na *et al*.,[10] retrospectively, studied 136 patients using the dosing methodology as described by Johnson *et al*.[8] Though only 27% of the patients were found to have a complete clinical response, 6% of these developed recurrence during the 6-month follow-up.

The exact underlying mechanism of intralesional immunotherapy is not completely understood. Intralesional immunotherapy has been shown to induce non-specific inflammatory signals attracting antigen-presenting cells, which further act upon HPV particles.[11] Previous studies

have demonstrated that intralesional immunotherapy with different types of skin antigens like mumps, Candida, or Trichophyton antigens may lead to resolution of warts.[12] Horn *et al*.[13] observed that patients who demonstrated at least a 5 mm response to a skin antigen and later received an a 0.3 mL dose of that antigen had a significantly greater resolution of the injected wart than those treated with interferon alone or saline. Additionally, some patients reported resolution of even those warts which were not injected. However, this trial was stopped prematurely as it involved an unblinded clinical assessment, and there appeared to be an increased rate of fever and myalgias in the patients treated with immunotherapy.

In our study, we found that among patients with genital warts, 43% (12/28) patients did not show any clinical improvement or showed worsening with the MMR immunotherapy. Meena *et al*.,[14] in their report, showed excellent response in two patients with genital warts treated with immunotherapy. A possible explanation to this varied response could be the type of HPV causing the genital warts. But there are no data in the existing literature regarding response of MMR vaccine to specific HPV types. Also, among patients with verruca plana, around 50% of the patient showed complete response with immunotherapy. Mohta *et al*.,[15] in their report, concluded that immunotherapy with MMR is superior to vitamin D3 in verruca plana.

There are a few limitations of this study. Firstly, this was an observational study, and no comparison groups were studied. Secondly, the treatment protocol is specific to the study setting. We performed a maximum of four treatment sessions, which might not be true for other patient settings. Moreover, the immunogenicity of MMR vaccine used in the present study might vary with vaccine used in other patient settings. Lastly, we did not collect immunization history of patients, and prior doses of MMR vaccine may influence the clinical outcome.

Conclusion

The findings of our study show that MMR appear to be an effective and safer option than traditional destructive treatments for cutaneous warts. Warts in younger patients and located on palmo-plantar surfaces and extremities responded favorably to MMR vaccine. The treatment was well tolerated by the patients as well. Future multi-centric, randomized, controlled, prospective trials are needed to evaluate the clinical effects and factors affecting the efficacy of this treatment.

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.

Author's contribution

RK and SS contributed to the initial conceptualization, critical revision of content, and final approval of the manuscript. RK and IA contributed to the initial draft of the manuscript and literature review. BS contributed in statistical analysis.

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Original Article

Treatment Results with 5-mm Surgical Excision in Nonmelanoma Skin Cancers: Analysis of 234 Cases

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Abstract

Background: Basal cell carcinoma and squamous cell carcinoma constitute the majority of nonmelanoma skin cancers. In our study, we analyzed our results of nonmelanoma skin cancer treatment with 5-mm surgical excision and compared them with the literature. **Material and Methods:** Patients treated at Ankara City Hospital Plastic, Reconstructive, and Aesthetic Surgery Clinic between February 2019 and March 2022 were included in this study. Demographic data, anatomical region, tumor subtype/differentiation, surgical margins, reconstruction method, and recurrence parameters were recorded. IBM SPSS Statistics (version 26.0) was used for the data analysis. **Results:** Of the 234 cases, 163 were reported as basal cell and 71 as squamous cell cancer. Margin positivity with 5-mm surgical excision was 14.1% and 16.9% in basal and squamous cell cancer, respectively. Nineth-month recurrence rates were 4.2% and 19.7% in basal and squamous cell cancer, respectively. **Conclusions:** All surgical margin positivity and recurrences were located in the head and neck regions, revealing the importance of developing treatment references according to the anatomical region.

Keywords: Basal cell cancer, local neoplasm recurrence, margins of excision, recurrence, skin neoplasms, squamous cell carcinoma

Introduction

Nonmelanoma skin cancers (NMSCs) include mainly basal cell cancer (BCC) and squamous cell cancer (SCC). Other NMSCs are rare, and adnexal tumors, Merkel cell tumors, and skin lymphomas can be considered examples. The incidence of NMSCs has increased by an average of 3%–8% per year since the 1960s.[1] This increase in incidence can be attributed to aging of the population, increased sun exposure, and increased diagnostic possibilities.[2]

Chronic sun exposure is the main factor affecting NMSC formation. Other causes include white skin, ionizing radiation, immunosuppression, previous malignancy, and conditions that predispose the patients to malignancy. The diagnosis of NMSC is usually clinically and histopathologically confirmed by excision. Histopathological diagnosis using punch biopsy is useful for large lesions that require graft or flap surgery.[3] The American National Association for Cancer Research (NCCN) defines NMSC as low or high risk according to its location, histological features, size, primary or recurrent occurrence, and presence of immunosuppression. According to this classification, a surgical margin of 4 mm for BCC and 4–6 mm for SCC, and postoperative margin evaluation are recommended for low-risk lesions. The gold standard for high-risk lesions is micrographically oriented histographic surgery (MOHS) surgery. Excision with wider surgical margins is recommended for cases in which MOHS surgery is not possible. However, the main disadvantage of MOHS surgery is that it is time-consuming and expensive.[2] Therefore, standard surgical excision remains important and is used for both low- and high-risk lesions. However, the wider surgical margin recommended for high-risk lesions increases morbidity because most lesions are located in the head and neck regions.

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The success of treatment and the accumulation of literature in this field are important, because NMSCs are common in the community and are important in terms of morbidity and treatment costs. The main purpose of our study was to evaluate the demographic factors and treatment success in patients who applied to our clinic and underwent 5-mm standard surgical excision and compare them with the existing literature.

Materials and Methods

Ethics committee approval (E1-22-2462, dated March 9, 2022) for the study was obtained from the local ethics committee of Ankara City Hospital. Patients who were treated with surgical excision in our clinic by scanning the hospital data record system with the diagnosis of "C44" international classification of diseases code between February 2019 and March 2022 in Ankara City Hospital were included in the study. First, this was a retrospective study. Patients treated for recurrence were excluded, and only those who underwent primary standard surgical excision were included in the study. The orientation of the pathologist was ensured by placing two marker sutures on the superior, medial, lateral, or inferior borders of the removed material as a standard and by documenting this situation. All surgical excisions were performed with a surgical margin of 5 mm from the lesion or 5 mm from induration around the lesion if existed. Patients diagnosed with cancers other than nonmelanocytic cancers in the final pathology report were excluded from the study. A total of 234 patients who met these criteria were identified. Tumors with the largest diameter and depth, more complex reconstruction, or positive surgical margins were considered in patient with more than one NMSC. Age, sex, anatomical region, tumor subtype and differentiation, reconstruction method, surgical margins, re-excision rate, and recurrence were recorded. Surgical margins were evaluated as either lateral and/or deep positive. During patient follow-up, the recurrence of the primary tumor, which was documented clinically and histopathologically, was considered recurrence. Patients were followed up clinically at the first, third, sixth, and ninth months for recurrence. IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. (Armonk, NY: IBM Corp) was used for the data analysis. Descriptive statistics were used for parameters such as age, sex, tumor subtype, differentiation, reconstruction method, margin positivity, and recurrences.

Results

Of the 234 patients, 163 (69.6%) were diagnosed with BCC and 71 (30.3%) were diagnosed with SCC. Concomitant NMSC was found in 24 (14.7%) cases diagnosed with BCC and 15 (21.1%) were diagnosed with SCC. Demographic data, tumor histopathological features, and tumor locations are summarized in Table 1.

Table 1: Demographic data and treatment results

Specifications	Nonmelanocytic cancer cases					
	n = 234					
Subtypes/Differantiation	BCC			SCC		
	n = 163			*n* = 71		
	Age = 68.5 (29–97, median = 70)			Age= 69 (40–94, median = 69)		
	Male/female ratio = 1.29			Male/female ratio = 1.44		
	Nodular		39 (23.9%)	Well differentiated		34 (47.8%)
	Infiltrating/morpheaform		14 (8.5%)	Intermediate differentiated		11 (15.4%)
	Nodulocystic		10 (6.1%)	Undefined		7 (7.8%)
	Superficial		8 (4.9%)	Insitu SCC (Bowen disease)		6 (8.4%)
	Micronodular		4 (2.4%)	Basosquamous		5 (7%)
	Mixt		37 (22.6%)	Undifferentiated		3 (4.2%)
	Undefined		40 (24.5%)	Other subtypes (sarcomatoid, clear cell, acantholytic, verrucous)		3 (4.2%)
	Other subtypes (Adenoid, nodulocystic, follicular)		11 (%6,3)			
Regions	Head and neck (*n* = 150)	Nose	62 (%38)	Head and neck (*n* = 57)	Nose	16 (%22,5)
		Malar-temporal	30 (%18,4)		Malar-temporal	17 (%23,9)
		Frontal/scalp	21 (%12,8)		Frontal/scalp	9 (%12,6)
		Buccal	11 (%6,7)		Ear/preauricular	7 (%9,8)
		Ear/preauricular	9 (%5,5)		Lower lip	4 (%5,6)
		Neck	8 (%4,9)		Buccal	2 (%2,8)
		Upper lip	5 (%3)		Upper lip/neck	2 (%2,8)
		Medial cantus	4 (%2,4)		Ear	2 (%3,9)
					Neck	2 (%3,9)
	Trunk and extremities (*n* = 13)	Trunk: 10		Trunk and extremities (*n* = 14)	Trunk: 3	
		Lower extremity: 3			Lower extremity:4	
					Upper extremity:7	

Table 2: Detailed analysis of recurrences

Specifications	Recurrences			
	n = 21			
Subtypes/differantiation	BCC		SCC	
	n = 7		*n* = 14	
	Male/female = 4/3		Male/female = 9/5	
	Nodular	-	Well differentiated	2
			Intermediate differentiated	5
	Infiltrating/morpheaform	3	Undifferentiated	2
	Mixt	2	Undefined	2
	Undefined	2	Other subtypes	3
Tumor depth (mm)	3.6 (min–max: 2–4)		5.9 (min–max: 2–8)	
Tumor length (mm)	10.6 (min–max: 7–15)		37.6 (min–max: 6–115)	
Margin positivity	Positive	4	Positive	9
	Negative	3	Negative	5
Regions	Nose	3	Nose	4
			Ear/preaurikular	4
	Malar-temporal	2	Skalp	3
	Ear/preauricular	1	Malar-temporal	2
	Upper lip	1	Servikal	1

Of the BCC tumors, 88 (53.9%) were treated with full-thickness skin graft (FTSG), 51 (31.2%) were primary, 19 (11.6%) were local flaps, and 5 were treated with other methods (Antia-Buch, split-thickness skin graft [STSG], wedge excision). Of the SCC tumors, 33 (46.4%) were FTSG, 16 (22.5%) were primary, 12 (16.9%) were STSG, 7 (9.8%) were reconstructed using local and regional flaps, and the remaining three cases were reconstructed using other methods.

The re-excision rate was 10.4% in BCC tumors due to close or positive surgical margins, and 15.4% in SCC tumors. The histopathological positivity rates for BCC and SCC re-excision were 29.4% and 54.5%, respectively. The dominant BCC subtypes with margin positivity were mixt and infiltrative, and nearly 50% of these cases (12/23) were located on the nose. Thirteen cases with margin positivity with BCC were followed up for clinic recurrence due to patient preference without re-excision and none of them had clinic recurrence. There was not any dominance on differentiation of SCC cases with margin positivity. However, most of these cases (5/12) were located on the nose. Nine of 12 margin-positive cases with SCC had undergone re-excision. The remaining three cases were followed up without re-excision. One case was followed with palliative treatment due to patient comorbidities, two cases received adjuvant radiotherapy, and one of them received chemotherapy too.

Margin positivity after 5-mm surgical excision was 14.1% and 16.9% in BCC and SCC, respectively. All surgical margin positivities for BCC and SCC were located in the head and neck regions, and 82% and 83.3% of these cases were located in high-risk areas, respectively. The recurrence rates during follow-up were 4.2% and 19.7% for BCC and SCC, respectively. All recurrences for both tumor types were located in the head and neck regions, and 71.4% and 57.1% of these cases were located in high-risk areas, respectively. Most of the recurrences are located in nasal region for BCC and scalp, preauricular, and nasal regions for SCC. The mean age was 65.3 (min–max: 43–84; SD: 12.3) for recurrent cases. Of the 21 recurrent cases, 15 were treated with FTSG and STSG, three with local flaps, and three with primary closure. Five of the 21 cases had a concomitant NMSC as a predisposant factor. Detailed data of recurrences are given in Table 2.

Discussion

BCC and SCC, which constitute the majority of NMSCs, are quite different in terms of clinical course, etiopathogenesis, and treatment approach.[1] Therefore, separate analyses were performed for BCC and SCC, which were categorized on the same group. Although their localization in high-risk areas was similar, SCC tumors were more frequently located in the extremities. Although the mean age was similar for both cancer types, the male predominance was more prominent in SCC tumors in terms of sex. The most common reconstruction method was FTSG for both tumor types. We used FTSG for color matching and convenience during the tumor follow-up. Nodular and mixed subtypes were dominant in BCC tumors, and well-differentiated subtypes were dominant in SCC tumors. Our recurrence rate for BCC in 9 months was nearly the same compared with the literature. However, our recurrence rate for SCC was more than twice high compared with the literature.

Considering the clinical studies on the Turkish Index in the literature, it has been observed that BCC cases are twice

as common as SCC cases.[4-6] Our results indicated similar results on the distribution of NMSCs. In the general literature, it is reported that BCC is observed four to five times more frequently than SCC.[2,7] In terms of subtypes, mixed and infiltrative subtypes were observed more frequently in this study. However, the nodular subtype was the dominant subtype in another study conducted in a similar population.[8] This finding supports the fact that mixed and infiltrative lesions are primarily treated with surgical excision.

Studies on optimal surgical margins have focused on lateral surgical margins. In a meta-analysis of BCC excisions, a surgical margin of 3 mm was recommended for the low-risk group and for lesions measuring less than or equal to 2 cm. A margin of 4–6 mm is recommended for high-risk groups and for lesions measuring greater than or equal to 2 cm. Considering the studies included in the meta-analysis, quite different results were reported between the number of incomplete excisions in excisions with a 5-mm surgical margin.[9] In one study included in the meta-analysis, incomplete excision with 5-mm excision was observed in 8 of 50 nasal BCC cases,[10] whereas in another study, all 46 cases located in the whole body were completely excised.[11] According to our results and literature, we believe that the anatomical location of BCC tumors is an important factor in incomplete excision.

In a margin study of SCC, a positive margin was reported in 14 (17.3%) of 81 cases of excisions made according to the NCCN criteria, 13 of these cases were reported to be located in the head and neck regions. However, its localization has not been fully elucidated.[12] Based on the results of our study and the literature, delayed reconstruction may be the preferred method in conditions where MOHS surgery cannot be performed, particularly for SCC tumors located especially in the head and neck regions. Similarly, delayed reconstruction or MOHS surgery is recommended for the treatment of high-risk lesions of both types.[3]

The 5-year recurrence rate in high-risk lesions with standard surgical excision has been reported to be 4.1%–10.1% in BCC and 8.1% in SCC.[2] In this respect, our early recurrence rates are more than twice as high for SCC compared with the literature. This may be due to the fact that tumor behavior is quite different in SCC compared with BCC. Additionally, since our all recurrences located in the head and neck regions, we believe that two important factors may play a role in our high recurrence rate. First, our patients tend to present at a later stage for treatment. Second, excisions tend to be made more thinner in the face and neck regions than in the other body parts, because preserving the neurovascular and aesthetic structures is an important objective in face and neck surgeries to reduce morbidities.

The limitations of our study include the relatively small number of cases compared with the incidence in the community, the relatively short follow-up period for recurrence, and the single-center nature of the study. We believe that conducting multicenter studies with longer follow-up periods will contribute to the accumulation of knowledge on this subject.

As a result, in the treatment of BCC and SCC, which constitute the majority of cases in the treatment of NMSCs, excision with a 5-mm surgical margin provides 95.8% and 80.3% treatment success in BCC and SCC, respectively. The positive surgical margin and recurrences were located in the head and neck regions, especially in high-risk areas in both tumor types. In conclusion, location-based treatment algorithm can increase treatment success and delayed reconstruction may be a preferred method for the treatment of tumors located in the head and neck regions.

Ethical approval

Ethical approval (E1-22-2462, date March 9, 2022) was obtained from the local ethics committee of Ankara City Hospital.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Keratoacanthoma Seen with Hidradenitis Suppurativa: A Case Report

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Abstract

Hidradenitis suppurativa (HS) is considered a primary disease of the hair follicle. The chronic occlusion of the follicular pilosebaceous unit and an associated immune response appears to be the main causes. The chronic, active, and poorly controlled disease may lead to several complications such as scars, contractures, lymphedema, osteomyelitis, and squamous cell carcinoma (SCC). We report here a 33-year-old male with HS who developed keratoacanthoma while on secukinumab treatment. The tumor representing 2 weeks of evolution in an area affected by HS (lower abdomen) was followed up after histopathological confirmation. Almost complete spontaneous regression was observed at the subsequent visits. As far as we are aware, solitary keratoacanthoma associated with HS has not been previously described. Our case shows that squamous differentiation is not limited to SCC and can develop from any scar tissue outside the anogenital region in patients with HS. Thus, the case presented here emphasizes the necessity of careful examination in scar areas as well as inflammatory lesions in HS.

Keywords: Biological therapy, hidradenitis suppurativa, keratoacanthoma, squamous cell carcinoma

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease characterized by deeply located painful nodules and abscesses, often result in sinus tracts and scarring. It frequently occurs after puberty, affecting 1% of the population. The chronic occlusion of the follicular pilosebaceous unit and an associated immune response appears to be the main causes.[1] The chronic, active, and poorly controlled disease may lead to several complications such as scars and squamous cell carcinoma (SCC).

Case Report

A 33-year-old male with a diagnosis of HS since 2012 applied to our clinic. Physical examination revealed multiple inflamed, tender, discrete papules and nodules with linear scars and fistulas. He was previously treated with systemic antibiotics and isotretinoin. He had 30 pack-years of smoking and genital human papillomavirus (HPV) infection. He was included in an ongoing study and started on biological therapy (secukinumab). With the initiation of secukinumab, he achieved clinical remission. After 4 months of therapy, a new (2 weeks old) 1×1.5 cm dome-shaped nodular lesion with a crateriform hyperkeratotic center in the intersection area of the abdomen and the pubic fold was seen [Figure 1a]. An incisional biopsy was taken with the suspicion of keratoacanthoma (KA) or SCC. Almost complete spontaneous regression was observed at the subsequent visit [Figure 1b] and KA diagnosis was established with biopsy [Figure 2].

Discussion

KAs, accepted as well-differentiated SCC, are mostly solitary, rapidly growing dome-shaped nodules containing central keratin plug. There is only one previous case

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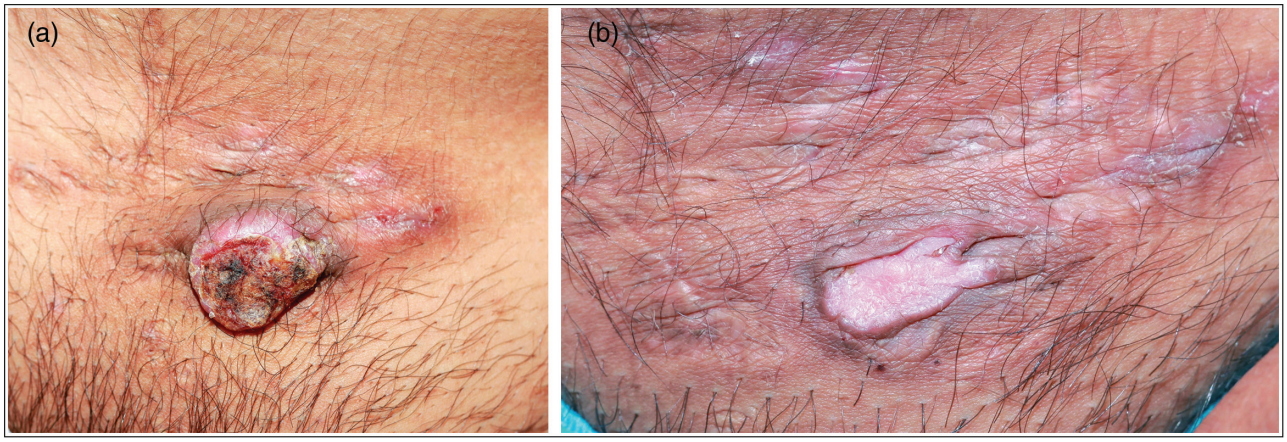

Figure 1: (a) A dome-shaped nodular lesion with a crateriform and hyperkeratotic center, measuring 1 × 1.5 cm in the intersection area of the abdomen and the pubic fold where patient has previous HS scars. (b) Ongoing assessment showed almost complete spontaneous regression of the lesion 12 weeks after the biopsy. The hyperkeratotic center was already cleared, and the lesion was flattened

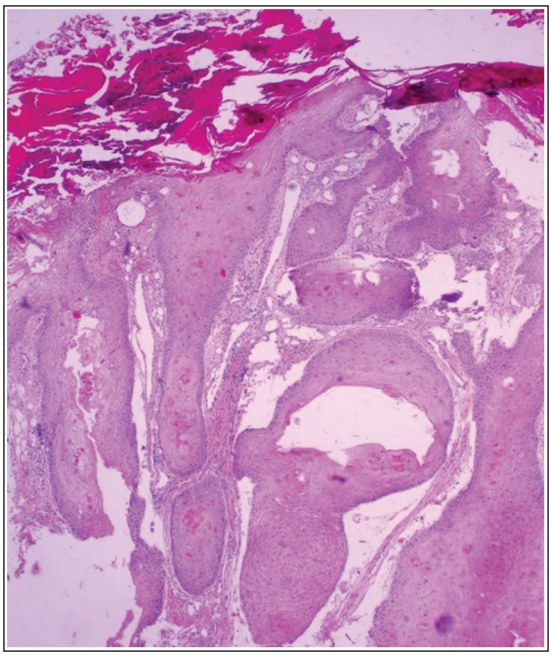

Figure 2: Biopsy shows some dysplastic cells with mitosis, absence of invasion, and nest and clusters of proliferating well-differentiating squamous epithelium (H&E X200).

report of co-occurrence of HS and KA published in the literature.[2] However, in that report, the patient had Dowling-Degos disease and multiple KAs along with HS. Fenske *et al.*[2] suggested that the association might be attributed to the common etiopathogenetic mechanism and a single underlying defect of the abnormal epithelial proliferation of the pilosebaceous apparatus as KAs also arise from hair follicles like HS. This underlying defect could be abnormal Notch signaling, which is an important protein for normal follicle development and skin appendages. Impaired Notch signaling disrupts hair follicle homeostasis and structure, leading to an inflammatory immune response like in HS.[3] Furthermore, Notch was shown to act as an epidermal tumor suppressor in nonmelanoma skin cancers, including SCC.

Another pathogenetic mechanism could be the concept of the immunocompromised cutaneous district.[4] Cutaneous scars are vulnerable sites for the development of neoplasms and dysimmune reactions. Caccavale *et al.*[4] suggested that the immunological behavior of a scarred area is different from that of the rest of the body. Thus, the scar area's destabilization could be a predisposing factor to tumors in HS. A recent literature review found 85 cases of SCC arising on scars in HS, mainly in men and in the anogenital region.[5]

The development of squamous tumors is likely multifactorial. Other well-described risk factors are smoking and HPV infection.[5] Smoking was reported to downregulate Notch signaling in airway epithelial cells, the pathway involved in HS and nonmelanoma skin cancers.[5] Thus, the effects of smoking may augment preexisting impairment of Notch signaling, which may increase susceptibility to SCC.[3]

Furthermore, according to Jourabchi *et al.*,[5] consideration should be given to the increasing use of biological immunosuppressants in HS and the association between chronic immunosuppression and tumors. Thus, secukinumab therapy might be an accelerating factor in our patient along with all these risk factors and pathomechanisms.

Our case shows that squamous differentiation is not limited to SCC and can develop from any scar tissue outside the anogenital region in patients with HS. Thus, the case presented here emphasizes the necessity of careful examination in scar areas as well as inflammatory lesions in HS.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Letter to the Editor

Lumps and Bumps Over Vulva

Dear Editor,

Vulval varicosities are more common in pregnancy, usually in the second half of pregnancy, accounting for 10%, which regresses on delivery.[1] It is generally asymptomatic, but may cause pelvic discomfort, vulval pressure, pruritus, or bleeding. We report this case of vulval varicosities for its rarity and infrequent presentation to dermatologists.

A 27-year-old woman, in the seventh month of her second pregnancy, presented to us with a history of multiple itchy reddish to purple swellings that become more evident on standing over the vulva for a 1-month duration. There was no history of any ulcer/genital scar/trauma before the onset of the lesion. There was no history of any surgery or use of oral contraceptives. There was no history of similar swelling in the previous pregnancy. On clinical examination, multiple non-tender, partially compressible, tortuous bluish swellings, somewhere combining to form a large swelling of size 3 cm × 4 cm present over the external surface of the right labia majora. Similar nodules were also seen on the inner aspect of the labia minora [Figure 1a and b]. Varicose veins were also seen on the medial aspect of the right thigh. On clinical examination, our differential diagnoses were vulval varicosities, pyogenic granuloma, and Bartholin cyst. Local ultrasonography followed by color doppler of the patient was suggestive of multiple dilated venous channels with no arteriovenous (AV) malformation [Figure 2]. Based on the aforementioned findings, a final diagnosis of vulval varicosities was reached. After counseling, the patient was referred to the obstetrics department for further management but lost to follow-up.

Hormonal influence and scarcity of valves in the pelvic region leading to pelvic venous hypertension increase chances of varicosities in pregnancy.[2] Doppler sonography is preferred to investigate AV malformation or deep vein thrombosis.[3] As the varicosities tend to regress in the postpartum period, it is managed conservatively and the patient is advised leg end elevation, left-sided sleeping position, and avoidance of prolonged periods of standing or sitting. Active treatment is required in cases of symptomatic varicosities, superficial thrombophlebitis, or if symptoms persist after 6 weeks of postpartum. Active treatment includes sclerotherapy with 1% sodium tetradecyl sulfate or local excision.[3]

We report this case to create awareness among dermatologists to avoid unnecessary investigations for diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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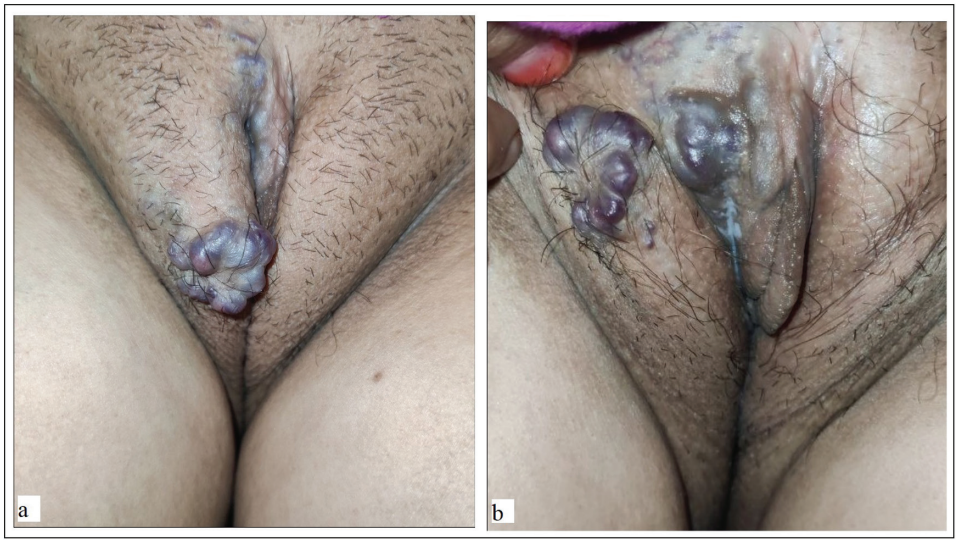

Figure 1: (a and b): Multiple non-tender, partially compressible, tortuous bluish swellings, to form a large swelling of size 3 cm × 4 cm present over the external surface of right labia majora (a) and inner aspect of labia minora (b)

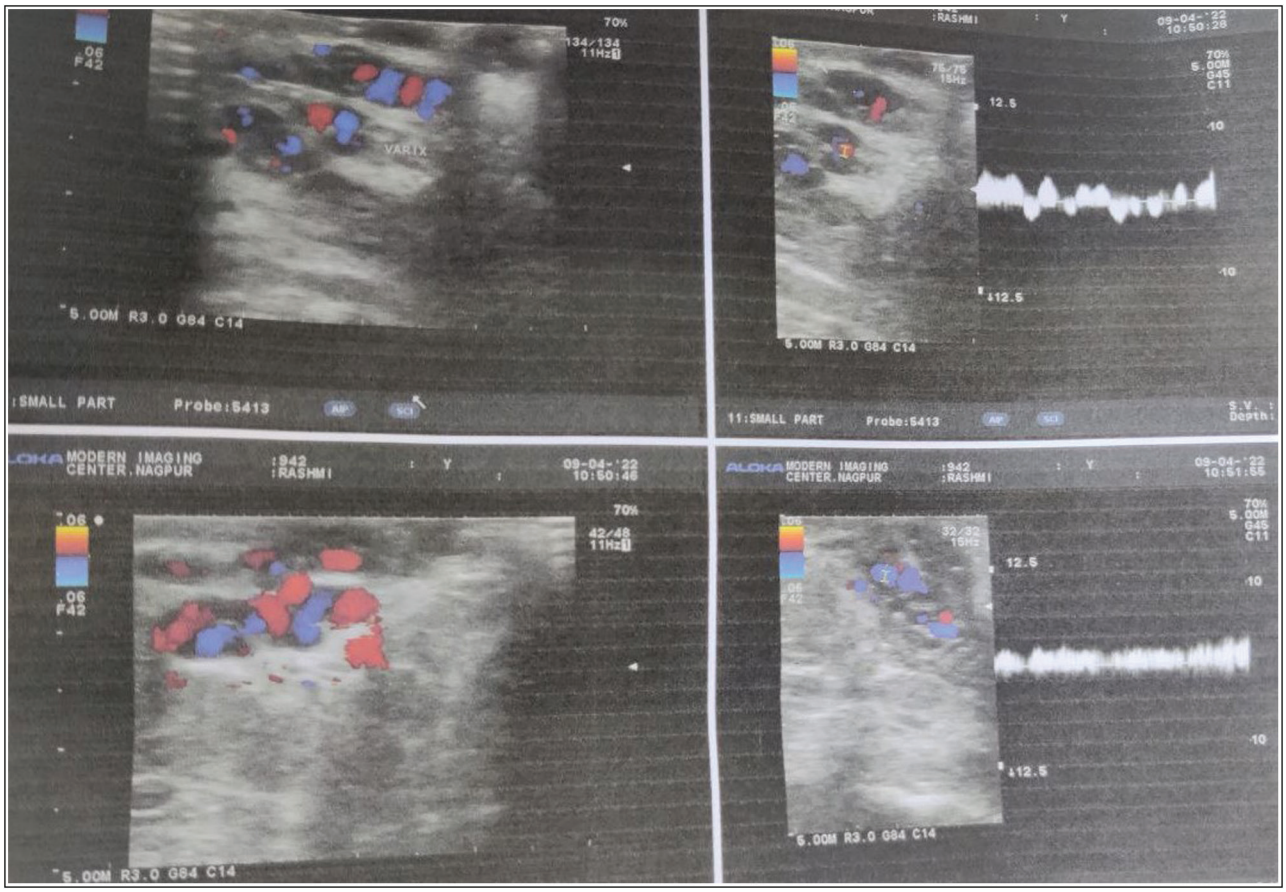

Figure 2: Multiple dilated venous channels with no arteriovenous malformation on right side of vulva

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