Original Article

Changes in the Clinical and Histopathological Features of Melanoma and Nonmelanoma Skin Cancers after COVID-19 Lockdown Period

Arzu Ferhatosmanoğlu, Leyla Baykal Selcuk, Şafak Ersöz[1], Esma Katkat Çelik, Faysal Keskin, Deniz Aksu Arıca

Departments of Dermatology and Venerology, [1]Pathology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Abstract

Introduction: Studies show that the number of skin cancers diagnosed and treated during the coronavirus disease 2019 (COVID-19) lockdown periods has decreased. **Objectives:** Comparing demographic and histopathological changes in skin cancer cases after the COVID-19 lockdown period with the prepandemic period. **Materials and Methods:** A retrospective observational study of skin cancers (basal cell carcinoma [BCC], squamous cell carcinoma [SCC], and malignant melanoma [MM]) diagnosed before the COVID-19 pandemic period (January 1, 2018–January 1, 2020) and after the COVID-19 pandemic period (June 1, 2022–January 1, 2023). A comparison was made between the two groups in terms of the duration of admission to the hospital, the tumor diameter at the time of admission, and the histopathological features of the tumor. **Results:** A total of 422 BCC, 257 SCC, and 67 MM cases were evaluated. After the COVID-19 pandemic period, the mean age at diagnosis was lower, and the mean time to diagnosis was shorter in BCC and SCC cases compared to the prepandemic period. There was no statistically significant difference in tumor thickness, tumor diameter, ulceration, lymphovascular invasion, or perineural invasion in nonmelanoma skin cancers before and after the COVID-19 pandemic. Although there was no significant difference between melanoma cases in terms of age, gender, mean duration of diagnosis, location, and presence of ulceration or mitosis, the rate of *in situ*/invasive melanoma increased in the post-COVID period. **Conclusions:** This study may allow an assessment that the COVID-19 lockdown period does not have a negative impact on skin cancers. However, for a more accurate assessment, studies with a larger sample size and longer follow-up periods are needed.

Keywords: Basal cell carcinoma, COVID-19, melanoma, prognosis, SARS-CoV-2, squamous cell carcinoma

Introduction

Skin cancers are the most common cancer in the United States.[1,2] Skin cancers cause significant morbidity and mortality each year.

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has so far affected nearly 661 million people worldwide.[3]

During the pandemic period, outpatient clinic applications were restricted by healthcare providers according to the urgency of the disease. Changes in outpatient clinic visits of skin cancer patients during this period have been reported in different studies in the literature. During the COVID-19 period, the decrease in patient applications in the lockdown period, the reduction in the number of dermatology outpatient clinics, the closure of wards, and the reduction in the number of surgical days may have led to a decrease in skin cancer diagnoses. For all patients with cancer, many faced delays in obtaining a diagnosis, whereas

Submission: 07-Jul-2023 **Revision:** 08-Nov-2023
Acceptance: 27-Nov-2023 **Web Publication:** 01-Feb-2024.

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_68_23

Address for correspondence: Dr. Arzu Ferhatosmanoğlu, Department of Dermatology and Venerology, School of Medicine, Karadeniz Technical University, Trabzon 61080, Turkey.
E-mail: arzuferhatosman@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Ferhatosmanoğlu A, Selcuk LB, Ersöz Ş, Çelik EK, Keskin F, Arıca DA. Changes in the clinical and histopathological features of melanoma and nonmelanoma skin cancers after COVID-19 lockdown period. Turk J Dermatol 2023;17:119-25.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

others experienced delays in starting or maintaining treatment.[4-6] Patient compliance with deferred visits also contributes to these numbers.[7] For skin cancer, the total number of lesions diagnosed and treated during lockdown periods decreased.[8]

The negative effects of the COVID-19 pandemic are diminishing in recent times, and many countries are lifting COVID-19 restrictions. This study aims to determine the demographic and histopathological changes in skin cancer cases during the postpandemic period compared to the prepandemic period.

In this study, a total of 746 patients who presented to the dermatology outpatient clinic and were histopathologically diagnosed with skin cancer (cutaneous squamous cell carcinoma [SCC], basal cell carcinoma [BCC], or malignant melanoma [MM]) were included. The objective was to assess whether there was a delay in the diagnosis of skin cancer during the normalization period after the COVID-19 pandemic compared to the prepandemic period, as well as to compare the histopathological characteristics of skin cancers. It should be noted that there has been no research examining the impact of the COVID-19 pandemic on skin cancers in our country, and international studies on this topic are limited.

Materials and Methods

The study included patients of all age groups who presented to dermatology clinics and were clinically and histopathologically diagnosed with cutaneous SCC, BCC, or MM. The individuals' names, surnames, age at diagnosis, gender, number of diagnosed skin cancers, type, lesion localization, and histopathological features of the tumor (tumor thickness, diameter, degree of differentiation, perineural and lymphovascular invasion status, etc.) were recorded.

From hospital records, all patients diagnosed with cutaneous SCC, BCC, or MM using the corresponding ICD codes between January 12018, and January 12020, and between June 12022, and January 12023, were screened. Histopathology reports of patients diagnosed with SCC, BCC, and MM were obtained from the Department of Medical Pathology. Skin cancers diagnosed between January 12018, and January 12020, were considered as the pre-COVID-19 pandemic period, while skin cancers diagnosed between June 12022, and January 12023, were considered as the post-COVID-19 pandemic period. A comparison was made between the two groups in terms of patients' time of hospital admission, tumor diameter at presentation, and histopathological characteristics of the tumor. Ethics approval for this study was obtained from the local ethics committee.

Statistical analysis

The analysis of the data was conducted using the SPSS 23.0 statistical package (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The descriptive statistics of the evaluation results were given as numbers and percentages for categorical variables, and mean and standard deviation for interval variables. The normality of interval variables was examined with the One-Sample Kolmogorov–Smirnov test. As the condition of normal distribution was not met, interval data were compared using the Mann–Whitney *U* test. The chi-square test was used in the analysis of the differences between the ratios of categorical variables in independent groups. The statistical significance level was accepted as $P < 0.05$.

Results

Characteristics of nonmelanoma skin cancers, such as gender, average age, average diagnosis time, and tumor size before and after the COVID period, are presented in Table 1. Characteristics of nonmelanoma skin cancers, such as tumor location and subtypes before and after the COVID period are presented in Supplementary Table 1.

Before the COVID pandemic, 195 cases of BCC were detected, which increased to 227 cases after the pandemic. Prior to the pandemic, 9 cases (13.2%) of BCC were infiltrative BCC, 39 cases (57.4%) were nodular BCC, 14 cases (20.6%) were ulceronodular BCC, and 6 cases (8.8%) were superficial BCC. Among the cases detected after the pandemic, 9 cases (4.0%)

Table 1: Characteristics of non-melanoma skin cancers pre- and post-COVID period

	Pre-COVID BCC, *n* (%)	Post-COVID BCC, *n* (%)	*P* value	Pre-COVID SCC, *n* (%)	Post-COVID SCC, *n* (%)	*P* value
Female, *n* (%)	79 (40.5%)	102 (44.9%)	0.360	37 (31.6%)	57 (40.7%)	0.132
Male, *n* (%)	116 (59.5%)	125 (55.1%)		80 (68.4%)	83 (59.3%)	
Average age (years), mean ± std. dev	70 ± 12.9	61.2 ± 18.2	**<0.001**	72.9 ± 13.4	72.2 ± 14.5	0.830
Average diagnostic time (months), mean ± std. dev	53.7 ± 89.2	29.4 ± 45.4	0.081	24.9 ± 54.9	23 ± 51	0.710
Average tumor size (cm), mean ± std. dev	1.4 ± 1.1	1.1 ± 0.8	**0.010**	2.7 ± 2.3	2.2 ± 2.1	**0.024**

* *P* value not be calculated

P values below 0.05 are considered statistically significant. Significant p values are colored in bold.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

were infiltrative, 103 cases (46.2%) were nodular, 99 cases (44.4%) were ulceronodular, and 12 cases (5.4%) were superficial BCC.

There was no significant gender difference observed for BCC (*P*:0.360); however, the average age at diagnosis for BCC was 70 ± 12.9 years before the pandemic and dropped to 61.2 ± 18.2 years after the pandemic ($P < 0.001$). The average diagnosis time was 53.7 ± 89.2 months before the pandemic, which shortened to 29.4 ± 45.4 months after the pandemic ($P = 0.081$).

Before the COVID pandemic, 117 cases of SCC were identified, which increased to 140 cases after the pandemic. Prior to the pandemic, 97 cases (82.9%) of SCC were invasive, and 20 cases (17.1%) were *in situ* SCC. Among the cases detected after the pandemic, 116 cases (82.9%) were invasive, and 24 cases (17.1%) were *in situ*.

There was no significant difference in gender for SCC before and after the pandemic ($P = 0.132$), and no significant difference was found in the average age at diagnosis ($P = 0.83$). The average diagnosis time was 24.9 ± 54.9 months before the pandemic and 23.0 ± 51.0 months after the pandemic ($P = 0.71$).

There were 30 cases of MM detected before the pandemic and 37 cases detected after the pandemic. Before the pandemic, 15 cases (50%) of MM were acral MM, 6 cases (20%) were superficial spreading invasive MM, and 6 cases (20%) were nodular MM. After the pandemic, 12 cases (32.4%) were nodular MM, 8 cases (21.6%) were superficial spreading invasive MM, 6 cases (16.2%) were acral MM, and 11 cases (29.7%) were *in situ* ($P < 0.001$).

Characteristics of MM cases before and after the COVID period, such as gender, average age, average diagnosis time, and tumor size, are presented in Table 2. Characteristics of MM cases, such as tumor location and subtypes before and after the COVID period, are presented in Supplementary Table 2.

Table 2: Characteristics of malignant melanoma cases before and after the COVID period

	Pre-COVID MM, *n* (%)	Post-COVID MM, *n* (%)	*P* value
Female, *n* (%)	15 (50%)	18 (48.6%)	1.000
Male, *n* (%)	15 (50%)	19 (51.4%)	
Average age (years), mean ± std. dev	64 ± 15	58.5 ± 22.8	0.427
Average diagnostic time (months), mean ± std. dev	18.3 ± 26.3	23.2 ± 33.6	0.615
Average tumor size (cm), mean ± std. dev	2.5 ± 1.9	2.4 ± 1.3	0.521

* *P* value not be calculated

When the pre- and postpandemic periods for MM were compared, there was no difference in the female/male ratio, mean age at diagnosis, and mean time at diagnosis. Prior to the pandemic, the most frequent MM location was the lower extremity (18 cases, 60%), while after the pandemic, the most frequent locations were the head and neck (14 cases, 37.8%), followed by the lower extremity (13 cases, 35.1%).

In all skin cancer cases, complaints of pain, burning, stinging, bleeding, itching, weakness, and for melanoma, blistering were questioned before and after COVID.

While bleeding was the most common complaint in BCC (59%) and SCC (67.2%) patients in the pre-COVID period, itching was the most common complaint in the post-COVID period (44.6% in BCC and 35.8% in SCC, respectively). In MM patients, the most common symptoms both before and after COVID were puffiness and bleeding, respectively (65% and 48.3% pre-COVID; 47.3% and 41.2% post-COVID, respectively).

The histopathological features of BCC, SCC, and MM pre- and post-COVID are summarized in Tables 3 and 4. There were no statistically significant differences in tumor thickness and tumor diameter for all three cancer types before and after the pandemic. The most common depth of tumor invasion in nonmelanocytic skin cancers (BCC and SCC) in the pre- and post-COVID periods was the deep reticular dermis. The number of melanoma cases with vertical and radial growth patterns in the pre and post-COVID period is the same (*P* = not be calculated).

In BCC patients, frontal field localization increased in the later period (23 [11.1%]) compared to the pre-COVID period (13 [7.1%]) ($P = 0.023$). Supplementary Table 3 summarizes the distribution of nonmelanoma skin cancers in the head and neck region in the pre and post-COVID period.

The comparison of demographic characteristics of patients diagnosed with BCC, SCC, and MM before and after COVID, as well as tumor subtypes and tumor locations according to gender, is summarized in Table 5.

In the study, female and male cases were compared among themselves before and after the pandemic. In terms of gender, no difference was observed between the tumor subtype and tumor locations in the pre and post-COVID period; the evaluation of average age, average diagnosis time, and tumor size is presented in Table 5.

In BCC cases in the post-COVID period, compared to the pre-COVID period, the diagnosis age was statistically significantly lower in both female and male cases (female $P = 0.019$, male $P = <0.001$, respectively). In females, the average diagnosis time for BCC was shorter in the post-COVID period compared to the pre-COVID period, and there was statistical significance ($P = 0.024$). In males,

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Table 3: Histopathologic features of nonmelanoma skin cancers pre- and post-COVID period

	Pre-COVID BCC, *n* (%)	Post-COVID BCC, *n* (%)	*P* value	Pre-COVID SCC, *n* (%)	Post-COVID SCC, *n* (%)	*P* value
Tumor thickness, (mm), mean ± std. dev	3.1 ± 2.9	3.1 ± 3.2	0.153	5.3 ± 4.2	6.7 ± 5.9	0.160
Tumor diameter (cm), mean ± std. dev	1.1 ± 0.8	1 ± 0.8	0.576	2.3 ± 2.1	2.3 ± 2.1	0.857
Tumor invasion depth			**<0.001**			*
1—Papillary dermis	10 (6.4%)	26 (13.5)		6 (7.7%)	11 (14.4%)	
2—Reticular dermis	21 (13.4%)	21(10.9%)		5 (6.4%)	8 (10.5%)	
3—Deep reticular dermis	85 (54.1%)	126 (65.3%)		44 (56.4%)	35 (46.1%)	
4—Subcutaneous fat tissue	41 (26.1%)	20 (10.4%)		21 (26.9%)	20 (26.3%)	
5—Muscular layer	0	0		2 (2.6%)	2 (2.6%)	
Ulceration, confirmed	117 (48.3)	125 (51.7%)	0.219	61 (63.5%)	70 (63.1%)	0.943
Lymphovascular invasion, confirmed	0	0		0	1 (0.9%)	0.491
Perineural invasion, confirmed	2 (1%)	5 (2.3%)	0.457	7 (6.1%)	9 (8.1%)	0.753
Histological differentiation						*
–High				52 (81.3%)	96 (83.5%)	
–Intermediate				11 (17.2%)	17 (14.8%)	
–Low				1 (1.6%)	2 (1.7%)	

* *P* value not be calculated

P values below 0.05 are considered statistically significant. Significant p values are colored in bold.

Table 4: Histopathologic features of malignant melanoma cases pre- and post-COVID period

	Pre-COVID MM, *n* (%)	Post-COVID MM, *n* (%)	*P* value
Tumor thickness (mm), mean ± std. dev	6.7 ± 7.2	8.3 ± 15.7	0.946
Tumor diameter (cm), mean ± std. dev	2.3 ± 1.7	2.5 ± 1.7	0.445
Ulceration, confirmed	22 (78.6%)	13 (54.2%)	0.116
Lymphovascular invasion, confirmed	1 (3.6%)	0	1.000
Perineural invasion, confirmed	0	0	*
Breslow thickness (mm), mean ± std. dev	7.7 ± 8.1	5.2 ± 3.7	0.409
Mitotic activity (..../mm^2), mean ± std. dev	6.5 ± 8.1	7.6 ± 7.3	0.347
Regression, confirmed	0	1 (4.5%)	0.449
Microsatellite, confirmed	3 (11.1%)	2 (9.5%)	1.000
Growth phase:			*
1—Vertical	9 (40.9%)	9 (42.9%)	
2—Radial	2 (9.1%)	2 (9.5%)	
3—Vertical and radial	11 (50%)	10 (47.6%)	
Intratumor lymphocyte:			0.291
1—None	9 (32.1%)	6 (28.6%)	
2—Mild	12 (42.9%)	13 (61.9%)	
3—Diffuse	7 (25%)	2 (9.5%)	

* *P* value not be calculated

in the post-COVID period compared to the pre-COVID period, the average BCC tumor size was smaller; there was statistical significance (*P* =0.036).

Discussion

In this study, we presented a comparison of melanoma and nonmelanoma skin cancers that we followed in a single center before and after the lockdown period due to COVID-19, examining their clinical and histopathological findings.

In a study, hospital admissions and surgical procedures for skin cancer patients have decreased persistently since the beginning of the pandemic in Germany.[9] In a study that collected data on the delay in cancer diagnosis due to the COVID-19 pandemic, the following was found: All cancer diagnoses fell in 2020 by 44.9% compared with 2018 and 2019. Melanoma and nonmelanoma skin cancer represented 56.7% of all missing diagnoses.[6]

Earnshaw *et al.*[8] found a 34.3% reduction in urgent skin cancer referrals in a retrospective review of a cancer tracking database in the UK from February to April 2020. Compared to previous years, the total number of skin cancers diagnosed in March 2020 was lower.

Nolan *et al.*,[10] a prospective cohort of patients undergoing nonmelanoma skin cancer surgery was undertaken. Retrospective data were collected on melanoma surgery. The number of NMSCs treated per week fell by

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Table 5: Comparison of changes in average age, average diagnosis time, and tumor size in the pre and post-COVID period according to gender

	Pre-COVID female, *n* (%)	Post-COVID female, *n* (%)	*P* value	Pre-COVID male, *n* (%)	Post-COVID male, *n* (%)	*P* value
BCC						
Average age (years), mean ± std. dev	68.2±12.9	61±18	**0.019**	71.3±12.9	61.5±18.3	**<0.001**
Average diagnostic time (months), mean ± std. dev	46.3±80.8	26.7±36.3	**0.024**	58.7±94.5	31.6±5.4	0.689
Average tumor size (cm), mean ± std. dev	1.3±1.1	1.1±0.9	0.107	1.5±1.1	1.2±0.8	**0.036**
SCC						
Average age (years), mean ± std. dev	76.6±14.2	75.2±14.6	0.574	71.2±12.8	70.2±14.3	0.903
Average diagnostic time (months), mean ± std. dev	30.1±73	14.5±14	0.248	29.9±65.8	18±26.1	0.633
Average tumor size (cm), mean ± std. dev	3.1±2.5	2.2±1.8	0.090	2.5±2.1	2.2±2.3	0.086
MM						
Average age (years), mean ± std. dev	66.6±14.8	57.7±21.6	0.187	61.3±15.3	59.3±24.5	0.782
Average diagnostic time (months), mean ± std. dev	20.4±32	25.8±35.8	0.288	16.2±20.6	20.5±32	0.825
Average tumor size (cm), mean ± std. dev	2.2±1.6	2.4±1.4	0.561	2.7±2.2	2.4±1.3	0.734

**P* value not be calculated

P values below 0.05 are considered statistically significant. Significant p values are colored in bold.

27%–47% throughout April and May. Overall, 77% of Mohs micrographic surgeons stopped procedures.

In another study in which all dermatological and surgical activities were examined retrospectively, compared to the previous year, surgical excisions increased by 31.7%, and SLNBs decreased by 29% during the lockdown period. Dermatologic follow-up decreased 30.2%, whereas surgical follow-up decreased 37%.[11]

In a retrospective, single-center case–control study comparing 531 patients treated for NMSC during the COVID-19 period in 2020 with the outcomes of 817 patients treated the previous year, a decrease in BCC and SCC cases detected in 2020 was found (*P*: 0.021). No difference was observed between the groups in terms of the time from initial diagnosis to definitive treatment and tumor locations.[12]

In a study comparing the same periods of 2019 and 2020, it was found that excised advanced skin cancers significantly increased in 2020.[13,14]

In our study, the changes in NMSCs in the pre and post-COVID periods have been discussed in detail. The lower average diagnosis age and shorter average diagnosis time in BCC and SCC cases detected in the postpandemic period compared to the prepandemic period can be associated with various reasons. The first may be the rapid return of outpatient services in our country and the acceptance of many outpatient applications. The second reason could be that patients notice changes in visible areas like the skin quickly due to an increase in their self-care and disease perceptions during this period, thus applying to a doctor in a shorter time. The third reason might be that after the end of the epidemic, patients could have been referred more to the relevant department due to lesions detected by other departments.

In our study, the lack of statistically significant differences in findings such as tumor thickness, tumor diameter, ulceration, lymphovascular invasion, and perineural invasion in NMSCs in the pre and post-COVID periods, may allow an evaluation that the COVID-19 period had no negative impact on NMSCs. However, for a more accurate assessment, long-term follow-up with a large number of samples would be appropriate.

In a retrospective study by Barruscotti *et al.*, it was revealed that the diagnosis of melanoma decreased by 60% compared to previous years during the 2020 quarantine period and that there was a 30% decrease in all dermatological surgical activities.[14] Ricci and colleagues compared melanomas diagnosed before and after the 54-day quarantine period and found features known as poor risk factors, such as thickness, ulceration, nodular subtype, increased in melanomas after the closure.[15]

In one study, they documented a significant reduction in the number of new melanoma diagnoses during the lockdown period, which increased again in the period immediately after the first strict COVID-19 lockdown.[16]

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

In a newly published study, cases were compared during the COVID lockdown period and the normalization period afterward. In a total of 119 melanoma cases, no difference was observed in terms of age, gender, incidence, location, presence of ulceration or mitosis, and the ratio of *in situ* to invasive melanoma. After the recovery of normal activity, it was seen that Breslow's thickness increased compared to the previous year.[17] Similarly, Drumm *et al.*[18] compared melanoma cases detected in 2019 and 2020. They have noted that the observed increased thickness, ulceration, and microsatellitosis rates in melanoma cases in 2020 support the theory of delayed melanoma diagnosis during and after the COVID-19 pandemic.

In the post-COVID period, the average age of diagnosis in MM cases has decreased, and the shortening of the diagnosis time may result from the rapid normalization of outpatient services in our country. Despite this, similar to the literature, there has been an increase in tumor diameter, tumor thickness, and nodular subtype in the post-COVID period, although not statistically significant. However, no significant difference was observed in terms of the presence of ulceration or mitosis. The ratio of *in situ* to invasive melanoma in our study increased in the post-COVID period.

Conclusion

In our study, no difference was observed in terms of gender, tumor subtype, and location in NMSCs in the pre and post-COVID periods. In the post-COVID period, although no statistical significance was observed, the average diagnosis time in NMSCs was lower, whereas it was higher in MM cases. The average age in BCC and MM cases was younger in the post-COVID period. The average tumor size in the post-COVID period was statistically significantly lower in NMSCs, and although not statistically significant, it was also lower in MM cases.

The COVID-19 pandemic restrictions are being lifted globally. This study may suggest that the adverse effect of the COVID-19 pandemic on skin cancers was less observed in our country. We believe that the continuity of outpatient services in the pre and post-COVID periods, the ability of patients to reach doctors quickly, as well as increased disease anxiety during the COVID period, and patients becoming more alert to changes in the skin contributed to this result.

However, more research is needed to fully reveal the impact of cancer diagnosis and potential delays on long-term survival during the pandemic. The results obtained are necessary to optimize early diagnosis of skin cancer and long-term outcomes for patients.

Ethical approval

Ethical approval for this study was received from the ethics committee of Karadeniz Technical University Faculty of Medicine.

Data availability statement

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

Author contributions

Conception or design of the work: Arzu Ferhatosmanoğlu and Leyla Baykal Selçuk, Data collection: Arzu Ferhatosmanoğlu, Leyla Baykal Selçuk, Şafak Ersöz, Esma Katkat Çelik, Faysal Keskin, Deniz Aksu Arıca, Data analysis and interpretation: Arzu Ferhatosmanoğlu and Leyla Baykal Selçuk Critical revision of the article: Arzu Ferhatosmanoğlu, Leyla Baykal Selçuk, Şafak Ersöz, Esma Katkat Çelik, Faysal Keskin, Deniz Aksu Arıca Final approval of the version to be published: Arzu Ferhatosmanoğlu and Leyla Baykal Selçuk.

Financial support and sponsorship

None.

Conflict of interest

None.

References

1. Guy GP, Thomas CC, Thompson T, Watson M, Massetti GM, Richardson LC, Centers for Disease Control and Prevention (CDC). Vital signs: Melanoma incidence and mortality trends and projections—United States, 1982–2030. MMWR Morb Mortal Wkly Rep 2015;64:591-6.
2. Guy GP, Machlin S, Ekwueme DU, Yabroff KR Prevalence and costs of skin cancer treatment in the US, 2002–2006 and 2007–2011. Am J Prev Med 2015;48:183-7.
3. World Health Organization. Number of COVID-19 cases reported to WHO. Available from: https://covid19.who.int/. [Last accessed on January 12, 2023].
4. Meredith JW, High KP, Freischlag JA. Preserving elective surgeries in the COVID-19 pandemic and the future. JAMA 2020;324:1725-6.
5. Patt D, Gordan L, Diaz M, Okon T, Grady L, Harmison M, *et al.* Impact of COVID-19 on cancer care: How the pandemic is delaying cancer diagnosis and treatment for American seniors. Clin Cancer Inform 2020;4:1059-71.
6. Ferrara G, De Vincentiis L, Ambrosini-Spaltro A, Barbareschi M, Bertolini V, Contato E, *et al.* Cancer diagnostic delay in Northern and Central Italy during the 2020 lockdown due to the coronavirus disease 2019 pandemic. Am J Clin Pathol 2020;155;64-8.
7. Harper CA, Satchell LP, Fido D, Latzman RD. Functional fear predicts public health compliance in the COVID-19 pandemic. Int J Ment Health Addict 2021;19:1875-88.
8. Earnshaw CH, Hunter HJA, mcmullen E, Griffiths CEM, Warren RB. Reduction in skin cancer diagnosis, and overall cancer referrals, during the COVID-19 pandemic. Br J Dermatol 2020;183:792-4.

9. Makaranka S, Scutt F, Rahman K. The impact of the COVID-19 pandemic on diagnosis of skin cancer cases in North Cancer Alliance and Scotland. Cureus 2022;14:e25019.
10. Nolan GS, Dunne JA, Kiely AL, Pritchard Jones RO, Gardiner M, Jain A, RSTNCOVID: Skin Collaborative. The effect of the COVID-19 pandemic on skin cancer surgery in the United Kingdom: A national, multi-centre, prospective cohort study and survey of plastic surgeons. Br J Surg 2020;107:e598-600.
11. Filoni A, Fiore PD, Cappellesso R, Dall'Olmo L, Salimian N, Spina R, *et al*. Management of melanoma patients during COVID-19 pandemic in an Italian skin unit. Dermatol Ther 2021;34:e14908.
12. Lembo F, Cecchino LR, Parisi D, Portincasa A. Nonmelanoma skin cancer in COVID-19 era: The Foggia experience. J Cutan Aesthet Surg 2022;15:436-8.
13. Valenti M, Pavia G, Gargiulo L, Facheris P, Nucca O, Mancini L, *et al*. Impact of delay in follow-up due to COVID-19 pandemic on skin cancer progression: A real-life experience from an Italian hub hospital. Int J Dermatol 2021;60:860-3.
14. Barruscotti S, Giorgini C, Brazzelli V, Vassallo C, Michelerio A, Klersy C, *et al*. A significant reduction in the diagnosis of melanoma during the COVID-19 lockdown in a third-level center in the Northern Italy. Dermatol Ther 2020;33:e1407.
15. Ricci F, Fania L, Paradisi A, Di Lella G, Pallotta S, Sobrino L, *et al*. Delayed melanoma diagnosis in the COVID-19 era: Increased Breslow thickness in primary melanomas seen after the COVID-19 lockdown. J Eur Acad Dermatol Venereol 2020;34:e778-9.
16. Troesch A, Magdalena H, Forchhammer S, Del Regno L, Lodde G, Turko P, *et al*. The impact of the COVID-19 pandemic on the diagnosis of cutaneous melanomas: A retrospective cohort study from five European skin cancer reference centres. J Eur Acad Dermatol Venereol 2023;37:922-31.
17. Gil-Pallares P, Figueroa-Silva O, Gil-Pallares ME, Vázquez-Bueno JA, Piñeyro-Molina F, Monteagudo B, *et al*. Did COVID-19 lockdown delay actually worsen melanoma prognosis? An Bras Dermatol 2023;98:176-80.
18. Drumm C, Griffin C, Van Baarsel S, Quigley C, Madden S, Naidoo J, *et al*. Response to Trepanowski *et al*.'s "Delays in melanoma presentation during the COVID-19 pandemic: A nationwide multi-institutional cohort study. J Am Acad Dermatol 2023;89:e223-4.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Supplementary Table 1: Characteristics of non-melanoma skin cancers pre- and post-COVID period

	Pre-COVID BCC, *n*(%)	Post-COVID BCC, *n*(%)	*P* value	Pre-COVID SCC, *n*(%)	Post-COVID SCC, *n*(%)	*P* value
Tumor location			*			*
1—Head and neck	182 (93.8%)	208 (91.6%)		91 (79.8%)	112 (80%)	
2—Upper extremity	2 (1%)	6 (2.6%)		15 (13.2%)	14 (10%)	
3—Lower extremity	2 (1%)	2 (0.9%)		7 (6.1%)	9 (6.4%)	
4—Trunk	8 (4.1%)	9 (4%)		1 (0.9%)	5 (3.6%)	
5—Genital	0	2 (0.9%)		0	0	
BCC subtypes, *n* (%)			*			
Infiltrative type	9 (13.2%)	9 (4%)				
Nodular type	39 (57.4%)	103 (46.2%)				
Ulceronodular type	14(20.6%)	99 (44.4%)				
Superficial type	6 (8.8)	12 (5.4%)				
Subtype not defined	127(65.1%)	4(1.8%)				
SCC subtypes, *n* (%)						1.000
Invasive SCC				97 (82.9%)	116 (82.9%)	
In situ SCC				20 (17.1%)	24 (17.1%)	

*P value not be calculated

Supplementary Table 2: Characteristics of malignant melanoma cases before and after the COVID period

	Pre-COVID MM, *n*(%)	Post-COVID MM, *n*(%)	*P* value
Tumor location			
1—Head and neck	6 (20%)	14 (37.8%)	*
2—Upper extremity	3 (10%)	4 (10.8%)	
3—Lower extremity	18 (60%)	13 (35.1%)	
4—Trunk	3 (10%)	6 (16.2%)	
5—Genital	0	0	
MM subtypes,n(%)			**0.001**
Superficial spreading invasive type	6 (20%)	8 (21,6%)	
Nodular type	6 (20%)	12 (32,4%)	
Acral type	15 (50%)	6 (16,2%)	
In situ type	0	11 (%29,7)	
Subtype not defined	3 (10%)	0	

*P value not be calculated

P values below 0.05 are considered statistically significant. Significant p values are colored in bold.

Supplementary Table 3: Distribution of nonmelanoma skin cancers in the head and neck region in the pre and post-COVID period

Tumor location	Pre-COVID BCC, *n*(%)	Post-COVID BCC, *n*(%)	*P* value	Pre-COVID SCC, *n*(%)	Post-COVID SCC, *n*(%)	*P* value
Head and neck	182 (93.8%)	208 (91.6%)	*	91 (79.8%)	112 (80%)	*
a—Frontal	13 (7.1%)	23 (11.1%)	**0.023**	5 (5.5%)	15 (13.4%)	*
b—Malar	26 (14.3%)	41 (19.7%)		14 (15.4%)	22 (19.6%)	
c—Eyelid	18 (9.9%)	12 (5.8%)		1 (1.1%)	7 (6.3%)	
d—Medial canthus	5 (2.7%)	10 (4.8%)		2 (2.2%)	1 (0.9%)	
e—Nose	75 (41.2%)	60 (28,8%)		21 (23.1%)	13 (11.6%)	
f—Chin	6 (3.3%)	6 (2.9%)		3 (3,3%)	0	
g—Lip	2 (1.1%)	6 (2.9%)		13 (14.3%)	19 (17%)	
h—Frontotemporal area	9 (4.9%)	13 (6.3%)		2 (2.2%)	5 (4.5%)	
i—Ear	9 (4.9%)	15 (7.2%)		15 (16.5%)	14 (12.5%)	
j—Scalp	11 (6.0%)	9 (4.3%)		12 (13.2%	16 (14.3%)	
k—Neck	8 (4.4%)	5 (2.4%)		3 (3.3%)	0	
l—Nasolabial	0	8 (3.8%)		0	0	

* *P* value not be calculated

P values below 0.05 are considered statistically significant. Significant p values are colored in bold.

Original Article

Effects of Delivery Method on Skin Diseases and Allergy Status: A Cross-Sectional Study

Zuhal Metin, Koray Durmaz[1]

Department of Dermatology, Faculty of Medicine, Kirsehir Ahi Evran University, Kirsehir, Turkey, [1]Department of Dermatology, Lokman Hekim Etlik Hospital, Ankara, Turkey

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Abstract

Background: Recent data support a relationship between gut microbiota and various chronic diseases, with emerging evidence indicating a similar association with skin microbiota. **Objective:** This study aimed to examine the impact of the delivery method on skin microbiota and explore its effects on skin diseases and allergies. Sociodemographic characteristics, which are potential factors impacting skin microbiota, were also considered to investigate this relationship. **Methods:** A cross-sectional study was conducted with 285 pediatric patients. The delivery method, allergy status, age, gender, consanguineous marriage, and parental smoking exposure (PSE) factors were questioned. The present diagnoses of the patients were also recorded. Categorical variables were analyzed using Chi-square analysis. **Results:** An increased risk of infectious skin diseases (ISDs) (viral, bacterial, fungal) and allergies has been observed in cesarean section (CS) ($P < 0.001$, $P = 0.057$). The risk of scabies was higher in normal delivery ($P = 0.032$). There was no significant relationship between the method of delivery and atopic or non-atopic dermatitis. For children born by CS, PSE, and allergies were identified as factors increasing the risk of atopic dermatitis ($P = 0.045$, $P = 0.018$). Allergic children born by CS exhibited a lower prevalence of ISD ($P = 0.037$). In addition, a decrease in ISDs from 21.2% to 10.3% was observed after 3 years of age in normal births ($P = 0.139$). **Conclusion:** Minimizing sociodemographic risk factors and creating a balanced and healthy microbiota, especially in early life, through personal and environmental measures, will be an important part of the treatment of skin diseases and allergies.

Keywords: Allergy, cesarean section, delivery method, microbiota, skin diseases

Introduction

The rise in cesarean deliveries and evolving disease patterns necessitate comparing conditions in individuals born through normal vaginal delivery (NVD) and cesarean section (CS). The shift in delivery preferences has prompted recent research, particularly in the past few decades, exploring the connection between the increased occurrence of atopic and allergic diseases and the chosen method of delivery.

Multiple studies have examined the link between delivery method and atopic-allergic diseases (e.g., asthma, allergic rhinitis, atopic dermatitis (AD), food allergy). CS is commonly identified as a risk factor for them.[1,2] Additionally, some studies propose that CS could also increase the risk of immune-related conditions like inflammatory bowel diseases, immune deficiencies, and connective tissue disorders.[3]

Various factors, including maternal and infant stress, variations in physiological and neurological pathways, and the activation of distinct hormonal pathways based on the delivery method, undoubtedly have diverse effects on the newborn's health. However, in addition to these factors, the microbiota variances attributed to the method of delivery hold distinct and paramount importance concerning newborn health. Recent studies

Submission: 04-Oct-2023 **Revision:** 20-Nov-2023
Acceptance: 28-Nov-2023 **Web Publication:** 01-Feb-2024.

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_105_23

Address for correspondence: Dr. Zuhal Metin, Department of Dermatology, Faculty of Medicine, Kirsehir Ahi Evran University, Bagbasi, Kirsehir 40100, Turkey.
E-mail: dr.zuhalmetin@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Metin Z, Durmaz K. Effects of delivery method on skin diseases and allergy status: A cross-sectional study. Turk J Dermatol 2023;17:126-31.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

underscore the significance of microbiota, particularly in allergic and immunological diseases. Considering the target disease group in our study, microbiota appears to be the most crucial factor influencing our results. Hence, our study will place particular emphasis on microbiota. However, it is crucial to know that the impact of the delivery method on the newborn is a multifactorial and complex process.

Microbiota play crucial roles in shaping the immune system, defending against pathogens, and forming a protective barrier.[4] However, if the microbiome balance is disrupted (known as dysbiosis), these functions can be affected, leading to various disorders. Extensive research has focused on the connection between dysbiosis of gut microbiota and chronic conditions like inflammatory bowel disease, endocrine disorders, and neurodegenerative diseases.[5,6] However, microorganisms also form the skin microbiota, acting as a protective barrier and influencing the immune function of the skin.[7] Imbalances in the commensal bacteria of the skin microbiota can alter the number and diversity of microorganisms on the skin. Consequently, this disruption can impair the skin's physical and immune barrier functions, potentially leading to the development of skin disorders.

Studies on the relationship between skin microbiota and diseases have increased recently, paralleling the research on gut microbiota. Diseases such as AD, seborrheic dermatitis, acne vulgaris, rosacea, and infectious skin diseases (ISD) have been the focus.[7,8] Considering the shared immune response system influenced by gut and skin microbiota, it is more accurate to assess their effects on diseases together. The significance of the gut-skin axis is evident in conditions like AD associated with food allergy, dermatitis herpetiformis linked to celiac disease, and psoriasis related to gluten intolerance.[8] Therefore, the interaction between the skin and gut is likely modulated by the common host immune system.

Both the skin and gut microbiota can be affected by various factors such as age, gender, genetic structure, chronic disease status, diet, drug use, method of delivery, etc.[9] The method of delivery is one of the most important factors. Infants delivered via CS are primarily colonized by commensal skin bacteria (such as Staphylococcus, Streptococcus, Corynebacterium, and Propionibacterium), while infants born vaginally acquire organisms from the vaginal flora (including Lactobacillus, Prevotella, Sneatia, Corynebacterium, and Candida albicans).[10] These microbiota variations, based on exposure to the mother's birth canal microflora, impact the Th1/Th2 balance and the anti-inflammatory cytokine response through interactions between bacterial/viral components and immune cell structures.[11] Consequently, besides the local and physical effects of microbiota composition, altered immune responses can lead to chronic systemic inflammatory conditions. This highlights how the delivery method, including microbiota, can contribute to a wide range of diseases.

Existing studies have primarily focused on exploring the link between delivery methods and allergic diseases, leaving a research gap regarding its association with skin diseases. In this study, a unique approach is taken by investigating the impact on skin diseases while simultaneously considering sociodemographic factors that can influence the skin microbiota, in conjunction with the delivery method.

Subjects and Methods

This cross-sectional prospective study included 285 pediatric patients under the age of 10 from Kirsehir Training and Research Hospital's dermatology outpatient clinic. Participation was voluntary, and informed consent was obtained from all parents. A questionnaire was administered to gather information on age, gender, consanguineous marriage (CM), family history of smoking, allergy-atopy status, and delivery methods. Only patients with a confirmed diagnosis of allergy-atopy, supported by the hospital information system, were included.

The study examined both antenatal and postnatal smoking exposure in relation to the family history of smoking. Parents who did not take sufficient precautions to avoid smoking in the presence of their children were categorized as parental smoking exposure (PSE).

The dermatologist recorded the current diagnoses of the patients. Along with addressing their specific concerns, patients underwent a comprehensive systemic dermatologic examination. Patients with additional dermatological diagnoses apart from the main diagnosis were excluded from the study.

Other dermatitis group diseases (seborrheic dermatitis, irritant contact dermatitis, nummular dermatitis, napkin dermatitis, neurodermatitis, and photocontact dermatitis), which do not contain any allergic and atopic components, were grouped as "non-atopic dermatitis (NAD)."

All bacterial, viral, and fungal skin infections were grouped together as ISD. On the other hand, scabies, which are slightly higher in number, was examined separately.

Efforts were made to minimize factors that could impact the flora. As a result, individuals who underwent emergency CS for any reason, experienced birth complications, or received antepartum or intrapartum antibiotics were excluded from the study. Non-inclusion criteria also involved individuals who did not breastfeed

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

for at least 6 months and those with a chronic disease in either the mother or child.

Dermatological diagnoses and allergy status were compared in children born via NVD and CS, considering sociodemographic characteristics.

Data analysis was performed using the SPSS 25.0 package program. Qualitative data were presented as numbers and percentages, while quantitative data were expressed as means with standard deviation. Chi-square analysis was used to assess differences between categorical variables. Further analysis of group differences was conducted using binary logistic regression. Statistical significance was set as $P < 0.05$.

Results

The mean age of 285 pediatric patients was 5.25 ± 2.92. The youngest patient was 4 months old and the oldest one was 10 years old. Statistical data on gender, age, CM, PSE, method of delivery, allergy status, and dermatological diagnoses are presented in Table 1.

Fifty-eight patients were found to have allergies related to pollen, dust, food, drugs, bee stings, allergic asthma, or allergic rhinitis. In the NAD group of 59 patients, there were diagnoses of seborrheic dermatitis, irritant contact dermatitis, nummular dermatitis, napkin dermatitis, neurodermatitis, and photocontact dermatitis.

About 34 (11.9%) patients had a viral infection (molluscum or verruca vulgaris), 14 (4.9%) patients had impetigo, and 18 (6.3%) patients had tinea or candida which were grouped as ISD. The "other diseases" group included patients with vitiligo, nevus, urticaria, acne vulgaris, hemangioma, and pityriasis alba.

Table 2 presents statistical data comparing delivery methods and diagnoses. Accordingly, allergy diagnoses were 3.3 times higher in those born by CS ($P < 0.001$, 95% CI = 1.695–6.472). No significant difference was found in both AD and NAD groups. However, scabies were found to be 2.4 times higher in those born by NVD ($P = 0.032$, 95% CI = 1.057–5.444). It was also noted that although not statistically significant, ISD were more common in those born by CS ($P = 0.057$).

A comparison of AD status in NVD and CS groups according to sociodemographic characteristics is shown in Table 3. Accordingly, the risk of AD was found to be significantly higher in children with PSE who were born by CS ($P = 0.045$). It was also observed that allergic children had a risk for AD in both NVD ($P = 0.076$) and CS ($P = 0.018$), but this risk was statistically significantly 3.1 times higher in CS delivery ($P = 0.038$, 95% CI = 1.065–9.139).

Table 4 illustrates the comparison of NAD status in the NVD and CS groups based on sociodemographic characteristics. Although not statistically significant, the results indicate that PSE may reduce the risk of NAD in children born by NVD ($P = 0.051$).

According to the ISD comparisons in Table 5, while not reaching statistical significance, the rate of ISD in children born by CS whose parents were consanguineous (10.5%) was lower than in those born to non-consanguineous parents (29.6%) ($P = 0.080$). Notably, the rate of ISD in the 0–3 age group in normal-born children decreased from 21.2% to 10.3% in children over 3 years of age ($P = 0.139$). Additionally, CS-born allergic children showed a significantly lower prevalence of ISD ($P = 0.037$).

Sociodemographic characteristics and allergy status did not significantly impact the occurrence of scabies

Table 1: Characteristics of the patients

Characteristics		*N*	%
Gender	Male	147	51.6%
	Female	138	48.4%
Age	0–3	205	71.9%
	>3	80	28.1%
CM	Yes	46	16.1%
	No	239	83.9%
PSE	Yes	143	50.2%
	No	142	49.8%
Mode of Delivery	Normal	124	43.5%
	Cesarean	161	56.5%
Allergy	Has	58	20.4%
	Not	227	79.6%
Dermatological Diagnosis	AD	75	26.3%
	NAD	59	20.7%
	ISD*	66	23.2%
	Scabies	27	9.5%
	Other Diseases	58	20.4%

*ISD = includes viral, bacterial and fungal skin infections. CM = consanguineous marriage, PSE = parental smoking exposure, AD = atopic dermatitis, NAD = non-atopic dermatitis, ISD = infectious skin diseases

Table 2: Comparisons of delivery methods and diagnoses

Diagnosis		Normal		Cesarean		*P* value
		n	%	*n*	%	
Allergy	has	13	10.5%	45	28.0%	<0.001
	not	111	89.5%	116	72.0%	
AD	has	32	25.8%	43	26.7%	0.864
	not	92	74.2%	118	73.3%	
NAD	has	26	21.0%	33	20.5%	0.923
	not	98	79.0%	128	79.5%	
ISD*	has	22	17.7%	44	27.3%	0.057
	not	102	82.3%	117	72.7%	
Scabies	has	17	13.7%	10	6.2%	0.032
	not	107	86.3%	151	93.8%	

*ISD = includes viral, bacterial and fungal skin infections, AD = atopic dermatitis, NAD = non-atopic dermatitis, ISD = infectious skin diseases

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Table 3: Comparisons of atopic dermatitis status in normal and cesarean delivery groups according to sociodemographic characteristics

Characteristics		Normal delivery					Cesarean delivery				
		Atopic dermatitis					Atopic dermatitis				
		has		not		*P* value	Has		not		*P* value
		n	%	*n*	%		*n*	%	*n*	%	
Gender	Female	13	21.3%	48	78.7%	0.260	24	31.2%	53	68.8%	0.221
	Male	19	30.2%	44	69.8%		19	22.6%	65	77.4%	
Age	0-3	19	22.4%	66	77.6%	0.194	34	28.3%	86	71.7%	0.425
	>3	13	33.3%	26	66.7%		9	22%	32	78%	
CM	Yes	8	29.6%	19	70.4%	0.608	4	21.1%	15	78.9%	0.553
	No	24	24.7%	73	75.3%		39	27.5%	103	72.5%	
PSE	Yes	19	29.7%	45	70.3%	0.308	27	33.8%	53	66.2%	0.045
	No	13	21.7%	47	78.3%		16	19.8%	65	80.2%	
Allergy	has	6	46.2%	7	53.8%	0.076	18	40%	27	60%	0.018
	not	26	23.4%	85	76.6%		25	21.6%	91	78.4%	

CM = consanguineous marriage, PSE = parental smoking exposure

Table 4: Comparisons of non-atopic dermatitis status in normal and cesarean delivery groups according to sociodemographic characteristics

Characteristics		Normal delivery					Cesarean delivery				
		Non-atopic dermatitis					Non-atopic dermatitis				
		has		not		*P* value	Has		not		*P* value
		n	%	*n*	%		*n*	%	*n*	%	
Gender	Female	14	23%	47	77%	0.593	14	18.2%	63	81.8%	0.486
	Male	12	19%	51	81%		19	22.6%	65	77.4%	
Age	0-3	18	21.2%	67	78.8%	0.933	26	21.7%	94	78.3%	0.529
	>3	8	20.5%	31	79.5%		7	17.1%	34	82.9%	
CM	Yes	4	14.8%	23	85.2%	0.375	4	21.1%	15	78.9%	.1.000*
	No	22	22.7%	75	77.3%		29	20.4%	113	79.6%	
PSE	Yes	9	14.1%	55	85.9%	0.051	14	17.5%	66	82.5%	0.349
	No	17	28.3%	43	71.7%		19	23.5%	62	76.5%	
Allergy	has	1	7.7%	12	92.3%	0.298*	7	15.6%	38	84.4%	0.333
	not	25	22.5%	86	77.5%		26	22.4%	90	77.6%	

*These have at least 1 cell with an expected count of less than 5. Therefore, the *P* value obtained from Fisher's Exact Test took precedence over Pearson's chi-square. CM = consanguineous marriage, PSE = parental smoking exposure

in both normal and cesarean deliveries. No significant relationship was found between sociodemographic characteristics and allergy status based on the mode of delivery.

Discussion

In recent studies, the relationship between delivery methods and atopic-allergic diseases has gained increased attention. Asthma, allergic rhinoconjunctivitis, AD, and food allergies have been extensively studied in this context.[1,2] In a meta-analysis conducted by Bager *et al*. with 26 studies, it was observed that CS moderately increases the risk of allergic rhinitis, asthma, and food allergy, but not inhalant atopy or AD.[12]

In our study, patients with various allergies were grouped together due to the low number of patients in each subtype. Comparing the delivery method and allergic conditions, it was found that CS birth carried a 3.3 times increased risk of developing allergies [Table 2]. Although the precise mechanisms underlying this relationship are still not clarified, it is clear that the early formation and maturation of the infant microbiome has a significant impact on immune system development and prevention of allergic diseases.

Some studies suggest a link between the delivery method and AD,[13] but most studies have not found conclusive evidence to support this association.[12,14,15] Of course, factors such as genetics, environment, age, and sociodemographic characteristics may influence this

Table 5: Comparisons of infectious skin diseases (viral, bacterial, fungal) in normal and cesarean delivery groups according to sociodemographic characteristics

Characteristics		Normal					Cesarean				
		ISD					ISD				
		Has		Not		*P* value	Has		Not		*P* value
		n	%	*n*	%		*n*	%	*n*	%	
Gender	Female	10	16.4%	51	83.6%	0.699	18	23.4%	59	76.6%	0.281
	Male	12	19%	51	81%		26	31%	58	69%	
Age	0-3	18	21.2%	67	78.8%	0.139	33	27.5%	87	72.5%	0.934
	>3	4	10.3%	35	89.7%		11	26.8%	30	73.2%	
CM	Yes	6	22.2%	21	77.8%	0.570*	2	10.5%	17	89.5%	0.080
	No	16	16.5%	81	83.5%		42	29.6%	100	70.4%	
PSE	Yes	14	21.9%	50	78.1%	0.213	19	23.8%	61	76.3%	0.311
	No	8	13.3%	52	86.7%		25	30.9%	56	69.1%	
Allergy	has	1	7.7%	12	92.3%	0.461*	7	15.6%	38	84.4%	0.037
	not	21	18.9%	90	81.1%		37	31.9%	79	68.1%	

*These have at least 1 cell with an expected count of less than 5. Therefore, the *P* value obtained from Fisher's Exact Test took precedence over Pearson's chi-square. ISD = infectious skin diseases, CM = consanguineous marriage, PSE = parental smoking exposure

relationship. In our study, no significant association was found between delivery method and AD (P = 0.864) [Table 2].

Sociodemographic characteristics and allergy status were also analyzed in normal and cesarean births separately for their impact on AD [Table 3]. Herein, PSE showed a significant association with increased AD in CS (P = 0.045). Literature suggests that active smoking and passive smoke exposure are linked to higher AD prevalence in children and adults.[16] Smoking likely contributes to AD indirectly by disrupting the microbiota, in addition to its direct effects on the immune system and skin barrier. Consequently, it can be concluded that PSE in CS-born patients may enhance AD susceptibility by influencing the microbiota, immune system, or underlying mechanisms.

In our study, it was observed that having allergies increased the rate of AD in both normal and CS delivery, but this risk was significantly 3.1 times higher in CS (P = 0.038, 95% CI = 1.065−9.139) [Table 3]. The mechanism behind AD is not fully understood, but factors such as gene interactions, skin barrier defects, infectious agents, host environments, and immunological responses are believed to play a role.[17] Recent research emphasizes the importance of allergens in AD.[18] The skin's immune response to allergens in AD involves complex processes, including both immediate IgE-mediated and delayed T-cell-mediated responses.[19] In this intricate mechanism influenced by multiple factors, a balanced microbiota associated with NVD seems to partially mitigate the occurrence of AD in individuals with allergies.

The study found that the delivery method had no effect on NAD similar to AD (P = 0.923) [Table 2]. However, unlike AD, allergy did not impact NAD, and NAD cases were less common in normally born children exposed to parental smoke [Table 4]. This unexpected effect of smoking on NAD contradicts existing literature, which indicates that smoking irritates the skin due to toxic substances and disrupts blood flow and skin oxygenation.[20] Although this result may be influenced by the limited number of patients in the study, it is worth investigating the distinct effects of smoking on the microbiota of normal and cesarean-born children through non-atopic pathways.

Although not statistically significant, ISD was more common in patients born by CS (27.3%) compared to NVD (17.7%) (P = 0.057) [Table 2]. Conversely, scabies cases were significantly more prevalent in those born by NVD (P = 0.032) [Table 2]. The association between the ISD and CS may be linked to disrupted microbiota and compromised immune response. However, distinct factors need to be considered for the scabies group. The higher incidence of scabies in NVD births could be attributed to differences in the mechanism of parasitic diseases or the presence of unique sociodemographic characteristics among those opting for normal birth, potentially leading to living in less hygienic and more crowded environments.

The infection rate in both the 0–3 and 3+ age groups was similar and high in CS, but it decreased from 21.2% to 10.3% in NVD [Table 5]. Studies on the gut microbiota indicate significant changes until the age of 2–3 years.[21] Zhu *et al*. demonstrated that the delivery method continues to affect skin microbiota even up to 10 years of age.[22] In this study, the decrease in cases of ISD among the 3+ age group born via NVD may be attributed to the gradual development of the microbiome, enhancing its physical and immunological protective functions over time. The elevated ISD rate in CS up to 10 years of age (26.8%) is likely due to the long-term impact of altered microbiota. However, to support these hypotheses, it will be necessary to obtain statistically significant results in more comprehensive studies.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Allergies were found to be associated with a decreased risk of ISD in patients delivered by CS ($P = 0.037$) [Table 5]. The exact immunological mechanism is unknown, but it is worth noting that attentive care provided to allergic children born via CS and their upbringing in a hygienic environment may have contributed to these results. Additionally, although our results were not statistically significant, further studies could examine whether CM has the potential to decrease the risk of ISD in CS ($P = 0.080$). It is important to consider that besides systemic and local factors, genetic and sociodemographic factors, as well as the limited number of patients, may have influenced our results.

Undoubtedly, the method of delivery affects the health of the newborn in the short or long term through microbiota or other pathways. While our study did not reveal a significant difference in both atopic and NAD groups, the result observed in infectious and allergic diseases suggests otherwise. Furthermore, the finding in our study that PSE raises the risk of AD in individuals born via CS underscores the complexity of the underlying pathophysiology. In conclusion, certain compensatory mechanisms may help mitigate the negative effects of the delivery method. Disruption of this compensation by an internal or external factor such as exposure to smoking may contribute to the occurrence of certain diseases. The variability in research findings, with some studies identifying CS birth as a risk for AD while others do not, could be attributed to these internal and external factors.

While we generally attribute the pathology caused by the method of delivery to dysbiosis, it is evident that, regardless of the etiology, the microbiota plays a crucial role in the compensatory mechanism, considering its systemic, local, and immunologic effects. Therefore, in addition to the standard treatments for diseases, establishing a balanced and healthy microbiota, particularly during early childhood, and maintaining its stability through personal and environmental measures will constitute a significant aspect of the treatment.

The present study has limitations. The statistical significance was adversely impacted by the division of patients into smaller groups due to the extensive examination of numerous factors and diseases within the same study. For this reason, diseases were compared in normal and cesarean delivery categories separately. Further studies involving a large number of patients, which will be conducted separately for certain diseases and factors, will yield more significant results.

Acknowledgments

The authors would like to thank Mustafa Metin, MD, and Bensu Onentasci Demir, MD, for support and feedback throughout this project.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connor EA, Frazier EA, *et al*. Caesarean section delivery and the risk of allergic disorders in childhood. Clin Exp Allergy 2005;35:1466-72.
2. Negele K, Heinrich J, Borte M, von Berg A, Schaaf B, Lehmann I, *et al*.; LISA Study Group. Mode of delivery and development of atopic disease during the first 2 years of life. Pediatr Allergy Immunol 2004;15:48-54.
3. Sevelsted A, Stokholm J, Bønnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. Pediatrics 2015;135:e92-8.
4. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science 2016;352:539-44.
5. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol 2018;11:1-10.
6. Patterson E, Ryan PM, Cryan JF, Dinan TG, Ross RP, Fitzgerald GF, *et al*. Gut microbiota, obesity and diabetes. Postgrad Med J 2016;92:286-300.
7. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143-55.
8. De Pessemier B, Grine L, Debaere M, Maes A, Paetzold B, Callewaert C. Gut–skin axis: Current knowledge of the interrelationship between microbial dysbiosis and skin conditions. Microorganisms 2021;9:353.
9. Cresci GA, Bawden E. Gut microbiome: What we do and don't know. Nutr Clin Pract 2015;30:734-46.
10. Coelho GDP, Ayres LFA, Barreto DS, Henriques BD, Prado MRMC, Passos CMD. Acquisition of microbiota according to the type of birth: An integrative review. Rev Lat Am Enfermagem 2021;29:e3446.
11. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: Missing immune deviation, reduced immune suppression, or both? Immunology 2004;112:352-63.
12. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: Meta-analyses. Clin Exp Allergy 2008;38:634-42.
13. Yu M, Han K, Kim DH, Nam GE. Atopic dermatitis is associated with Caesarean sections in Korean adolescents, but asthma is not. Acta Paediatr 2015;104:1253-8.
14. Papathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. Pediatr Allergy Immunol 2016;27:419-24.
15. Richards M, Ferber J, Chen H, Swor E, Quesenberry CP, Li DK, *et al*. Caesarean delivery and the risk of atopic dermatitis in children. Clin Exp Allergy 2020;50:805-14.
16. Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: A systematic review and meta-analysis. J Am Acad Dermatol 2016;75:1119-1125.e1.
17. Novak N, Bieber T, Leung DYM. Immune mechanisms leading to atopic dermatitis. J Allergy Clin Immunol 2003;112:S128-39.
18. Caubet J-C, Eigenmann PA. Allergic triggers in atopic dermatitis. Immunol Allergy Clin North Am 2010;30:289-307.
19. Prescott VE, Forbes E, Foster PS, Matthaei K, Hogan SP. Mechanistic analysis of experimental food allergen-induced cutaneous reactions. J Leukoc Biol 2006;80:258-66.
20. Leow Y, Maibach HI. Cigarette smoking, cutaneous vasculature, and tissue oxygen. Clin Dermatol 1998;16:579-84.
21. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, *et al*. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 2018;562:583-8.
22. Zhu T, Liu X, Kong FQ, Duan YY, Yee AL, Kim M, *et al*. Age and mothers: Potent influences of children's skin microbiota. J Invest Dermatol 2019;139:2497-2505.e6.

Original Article

Evaluation of Oxidative Stress Levels as Biomarkers in Vitiligo Patients

Zeynep İnce, Büşra Kutlu[1], Kübra Bozali[2], Nazan Yılmaz[3], Fatma P. Cengiz[4], Eray M. Güler[2,5]

Department of Bioengineering, Faculty of Engineering and Natural Sciences, Bursa Technical University, Bursa, Turkey, [1]Medical Faculty, Bezmialem Vakıf University, İstanbul, Turkey, [2]Department of Medical Biochemistry, Hamidiye Faculty of Medicine, University of Health Sciences, Uskudar, Istanbul, Turkey, [3]Liv Hospital, Dermatology Clinic, Ulus, Istanbul, Turkey, [4]Department of Dermatology, Bezmialem Vakif University, Fatih, Istanbul, Turkey, [5]Department of Medical Biochemistry, Haydarpasa Numune Health Application and Research Center, University of Health Sciences, Uskudar, Istanbul, Turkey

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

Abstract

Objective: Vitiligo is a skin disease that causes the loss of melanocyte cells, which produce pigment in the skin. There is evidence that oxidative stress plays an important role in vitiligo disease of unknown pathogenesis. Evidence suggests that there is increased oxidative stress in melanocytes in patients with vitiligo. The aim of this study is to investigate oxidative stress markers in patients with vitiligo. **Materials and Methods:** Blood samples were taken from 23 vitiligo patients and 23 healthy control groups without any disease in Bezmialem Vakıf University Hospital Dermatology and Venereal Diseases Outpatient Clinic. Total antioxidant levels (TAS) and total oxidant levels (TOS) were measured photometrically method with blood samples. The oxidative stress index (OSI) was calculated as the TOS to TAS level ratio. **Results:** When the results of the vitiligo patient group were compared with the control group, TOS and OSI were found to be significantly higher than the control group ($P < 0.05$). No statistically significant result was found in TAS. **Conclusions:** Our results show that oxidative stress plays a role in the pathogenesis of vitiligo.

Keywords: Antioxidant, oxidant, oxidative stress, vitiligo

Introduction

Vitiligo is a dermatological disease characterized by limited depigmented patches resulting from the functional loss of melanocyte cells in the epidermis.[1] This condition typically manifests as non-scaly, chalk-white spots and is caused by selective melanocyte loss.[2] Studies on the epidemiology of vitiligo have found a wide range of incidence rates (0.14%–8.8%). However, the generally accepted view is that the incidence of vitiligo falls within the range of 1%–2%.[3] This disease is not associated with factors such as gender, age, or climate and can occur in individuals of all races. Nevertheless, it is more prevalent in individuals with a family history of vitiligo and those influenced by genetic factors.[4] The exact pathogenesis of vitiligo is not fully understood. Still, it is believed that genetic predisposition, autoimmune melanocyte damage, significant stress, infection, physical trauma, sunburn, and other factors may play significant roles in the disease's pathogenesis. Positive family history has been detected in 25%–50% of patients diagnosed with vitiligo.[5]

Vitiligo is characterized by acquired hypopigmentation and depigmentation, which can be attributed to several potential causes. These causes may include stress, accumulation of toxic compounds, infections, autoimmunity, mutations, melatonin receptor dysfunction, cellular microenvironmental changes, and disturbances in melanocyte migration and/or proliferation.[6]

Oxidative stress occurs due to imbalances in the production and degradation of reactive oxygen species

Submission: 17-Sep-2023 **Acceptance:** 19-Dec-2023
Web Publication: 01-Feb-2024.

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_95_23

Address for correspondence: Dr. Eray Metin Guler, Department of Medical Biochemistry, Hamidiye Faculty of Medicine, University of Health Sciences, Istanbul, Turkey.
E-mail: eraymetinguler@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: İnce Z, Kutlu B, Bozali K, Yılmaz N, Cengiz FP, Güler EM. Evaluation of oxidative stress levels as biomarkers in vitiligo patients. Turk J Dermatol 2023;17:132-5.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

(ROS). This condition is characterized by the oxidation and damage of biomolecules such as DNA, membrane lipids, enzymes, and structural proteins that cells cannot adequately repair.[7] Oxidative stress may play a significant pathogenic role in vitiligo. Some studies have shown that the accumulation of free radicals, which are toxic to melanocytes, leads to their destruction. Additionally, increased levels of nitric oxide have been observed in cultured melanocytes and the serum of vitiligo patients, suggesting that nitric oxide may contribute to the self-destruction of melanocytes. It has also been found that the red cells of vitiligo patients have lower levels of glutathione than control subjects, which helps prevent damage caused by free radicals. Therefore, vitiligo patients may experience higher levels of oxidative stress.[8] Our study aims to investigate the effects of vitiligo on oxidative stress.

Materials and Methods

This study was conducted in collaboration with the Dermatology and Venereology Clinic of Bezmialem Vakif University Hospital and the Department of Medical Biochemistry at Hamidiye Medical Faculty of Health Sciences University, following the approval of institutional ethical clearance with registration number 22/594.

Forty-six individuals were included in the study after obtaining informed consent. The study consisted of two groups: 23 vitiligo patients diagnosed clinically based on inclusion criteria and 23 voluntary control subjects. Inclusion criteria considered individuals under the age of 65 with no metabolic or skin diseases that share the same demographic characteristics as vitiligo and who do not consume alcohol and/or smoke. After the clinical examinations of all participants in the study groups, blood samples were collected for further analysis.

Blood samples

Blood samples were collected in gel clot activator sterile biochemical tubes. After centrifugation at 3000 × *g* for 10 min, the separated serum was stored at −80°C until further analysis.

Oxidative Stress Analysis

Determination of total antioxidant status

Measurement of Serum Total Antioxidant Status (TAS) is an automated method developed by Erel, which measures the total antioxidant capacity of the sample against strong free radicals.[9] In this method, 1 mM Ascorbic acid was used as a standard. Serum samples were measured in two stages using the Agilent Synergy HTX Multi-Mode Microplate Reader device at 660 nm. TAS results were expressed in mmol Ascorbic Acid Equivalent units per liter (mmol AA Eq/L).

Determination of total oxidant status

Measurement of Serum Total Oxidant Status (TOS) was measured using an automated measurement method developed by Erel. The color intensity, which can be measured spectrophotometrically, is associated with the total amount of oxidant molecules in the sample.[10] Hydrogen peroxide (H_2O_2) was used as the standard in this method. Serum samples were measured in two stages using the Agilent Synergy HTX Multi-Mode Microplate Reader device at 571/658 nm. TOS results were expressed in units of μmol H_2O_2 Equivalent per liter (μmol H_2O_2 Eq/L).

The oxidative stress index (OSI) in the samples was calculated as the ratio of TOS level to TAS level.

Statistical analysis

IBM SPSS version 28.0 software was used for statistical analysis. Mean ± standard deviation values were used to represent continuous variables. Mann–Whitney *U* test was performed to compare variables between the two groups. The relationships between variables were examined using Spearman's correlation coefficient. Confidence intervals (95%) were used to demonstrate differences between groups. Statistical significance was defined as $P < 0.05$.

Results

The TAS, TOS, and OSI parameters were compared between the Vitiligo and control groups [Figures 1–3]. As seen in Figure 1, TAS was lower in Vitiligo patients compared to the healthy control group, but this relationship was not statistically significant. However, TOS and OSI were significantly higher in Vitiligo patients compared to the control group ($P < 0.05$) [Figures 2 and 3].

The duration of vitiligo diagnosis for patients was recorded in months. The correlation between BMI, TAS, TOS, and OSI values with the duration of vitiligo diagnosis was

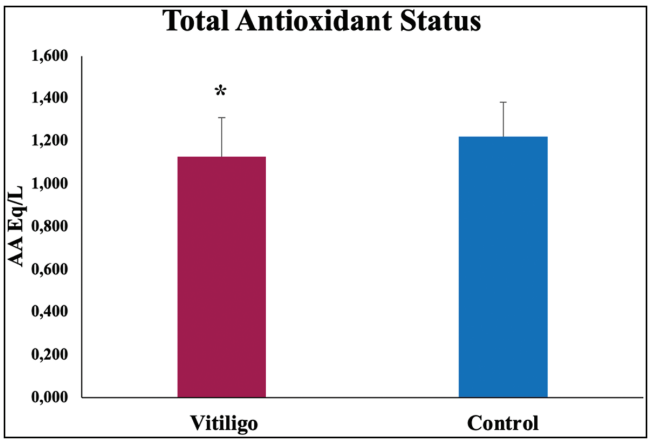


Figure 1: Total antioxidant status of vitiligo patients and healthy control group. Data are expressed as mean ± standard deviation ($n = 23$)

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

evaluated using the Spearman correlation test [Table 1]. No statistically significant correlations were found.

Discussion

Vitiligo is a disease characterized by the destruction of skin pigmentation and presents with depigmentation. The prevalence of vitiligo in Turkey is reported to be between 0.15% and 0.32%.[11] Familial cases of vitiligo are common, indicating a genetic predisposition, as 6% to 38% of vitiligo patients have affected family members.[12] The patches are initially small but expand over time. Skin lesions are predominantly observed on the face, hands, and wrists. Patients suffering from this disease often experience concomitant depression.[13]

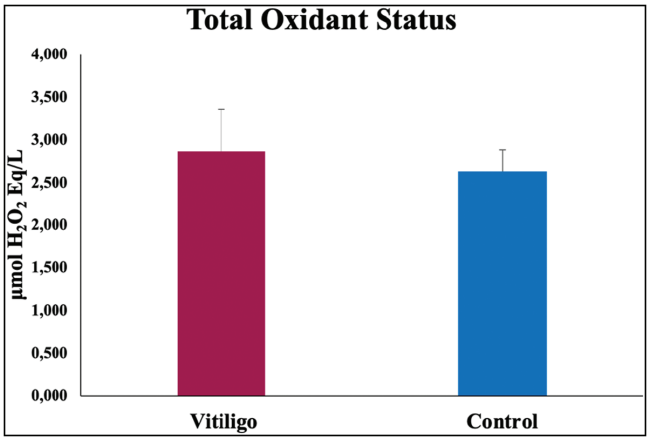


Figure 2: Total oxidant status of vitiligo patients and healthy control group. Data are presented as mean ± standard deviation (n = 23)

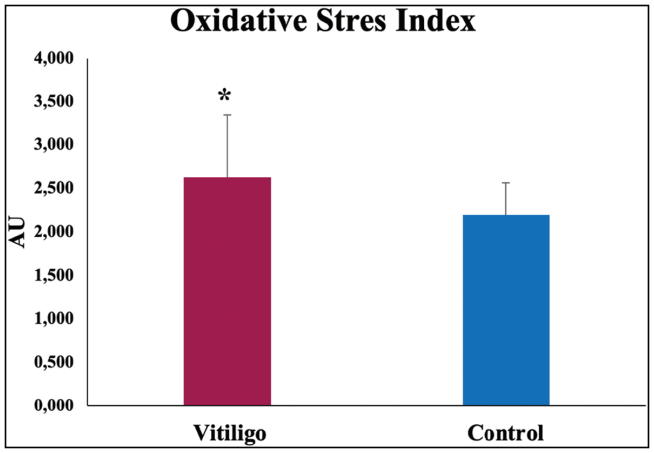


Figure 3: Oxidative stress index levels of vitiligo patients and healthy control group. Data are presented as mean ± standard deviation (n = 23). Differences in the vitiligo patient group were considered statistically significant at *P < 0.05, **P < 0.01, ***P < 0.001

Increased stress, life changes such as job loss, loss of a loved one, accidents, or illnesses, and physical traumas like exposure to ultraviolet (UV) radiation and pressure, contribute to the development or progression of vitiligo lesions. A study including five thousand vitiligo patients identified triggering factors in 51.4% of cases related to dietary factors, 34.26% to recurrent infections, 23.26% to medications, and 20.46% to emotional stress.[14]

Oxidative stress is characterized by forming and accumulating ROS, known as free radicals, during normal cellular processes. It leads to oxidative damage to cell membranes, proteins, lipids, and nucleic acids.[15] It is considered one of the possible pathogenic events in melanocyte loss. Defective recycling of tetrahydrobiopterin in the entire epidermis of vitiligo patients is associated with intracellular production of H_2O_2. Additionally, increased intracellular ROS production due to mitochondrial dysfunction and compromised antioxidant status supports the concept of systemic oxidative stress in vitiligo. This accumulated oxidative stress leads to DNA damage, lipid and protein peroxidation. Many proteins are modified through H_2O_2-mediated oxidation and exhibit partial or complete loss of functionality.[16]

Information obtained from different studies indicates that melanocyte loss in vitiligo results from increased epidermal oxidative stress through cytotoxic metabolites of melanogenesis. Several studies have demonstrated abnormalities in the antioxidant system and increased susceptibility of melanocytes to oxidative stress in the blood and skin of vitiligo patients.[17] Previous studies have shown the involvement of oxidative stress in the pathogenesis of vitiligo and higher levels of oxidative stress in vitiligo patients compared to the control group.[16,18] Our study yielded similar experimental results, although statistically significant findings were not obtained.

Furthermore, when considering the duration of vitiligo diagnosis in patients, no correlation was found between BMI, TAS, TOS, OSI parameters, and the duration of diagnosis.

Table 1: Correlation between BMI, TAS, TOS, and OSI in patients diagnosed with vitiligo

Correlation Parameters	BMI		TAS		TOS		OSI	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Vitiligo diagnosis (Months)	0,317	0,140	0,195	0,374	-0,071	0,748	-0,167	0,447

BMI: Body Mass Index, TAS: Total Antioxidant Status, TOS: Total Oxidant Level, OSI: Oxidative Stress Index, r: Spearman correlation coefficient

Conclusion

The results indicate oxidative stress's involvement in the pathogenesis of vitiligo.

Limitations

One limitation of this study is the small sample size in both groups, which may affect the generalizability of the findings.

Ethics committee approval

This study was conducted in collaboration with the Dermatology and Venereology Clinic of Bezmialem Vakif University Hospital and the Department of Medical Biochemistry at Hamidiye Medical Faculty of Health Sciences University, following the approval of institutional ethical clearance with registration number 22/594.

Acknowledgments

I am grateful to my valuable teachers Sümeyye AKIN KOÇ and Hakan BEYAZTAŞ for their valuable help during my study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Colucci R, Dragoni F, Moretti S. Oxidative stress and immune system in vitiligo and thyroid diseases. Oxid Med Cell Longevity 2015;2015:631927. doi: 10.1155/2015/631927.
2. Bergqvist C, Ezzedine K. Vitiligo: A review. Dermatology, 2020;236:571-592.
3. Bahadir S, Yayli S. Çocuklarda vitiligo: Epidemiyoloji ve etyoloji. Türkderm-Deri Hastalıkları ve Frengi Arşivi 2006;40:81-6.
4. Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: A comprehensive overview: Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol 2011;65:473-491.
5. Hayran, Y. Non-Segmental Vitiligo ile HLA Genotipi Ve Oksidatif Stres Arasındaki İlişki. 2019.
6. Taïeb A. Intrinsic and extrinsic pathomechanisms in vitiligo. Pigment Cell Res 2000;13:41-7.
7. Gutteridge JM, Halliwell B. In Free Radicals in Biology and Medicine. USA: Oxford University Press; 2015.
8. Halder RM, Chappell JL. Vitiligo update. Seminars in Cutaneous Medicine and Surgery. WB Saunders; 2009. p. 86-92.
9. Guler EM, Kurtulmus A, Gul AZ, Kocyigit A, Kirpinar I. Oxidative stress and schizophrenia: A comparative cross-sectional study of multiple oxidative markers in patients and their first-degree relatives. Int J Clin Pract 2021;75:e14711.
10. Motor S, Ozturk S, Ozcan O, Gurpinar AB, Can Y, Yuksel R, *et al*. Evaluation of total antioxidant status, total oxidant status and oxidative stress index in patients with alopecia areata. Int J Clin Exp Med 2014;7:1089-93.
11. Erman H, Toprak AE, Dürüyen S, Orhun A, Ocakoglu İ, Cengiz M, *et al*. İstanbul Medeniyet Üniversitesi Göztepe Eğitim Ve Araştırma Hastanesinde Vitiligo Hastalarında Tiroid Fonksiyonları ve Otoantikorları. Int J Basic Clin Med 2015;3:106-11.
12. Kemp EH, Gavalas NG, Gawkrodger DJ, Weetman AP. Autoantibody responses to melanocytes in the depigmenting skin disease vitiligo. Autoimmun Rev 2007;6:138-142.
13. Ghafourian E, Ghafourian S, Sadeghifard N, Mohebi R, Shokoohini Y, Nezamoleslami S, *et al*. Vitiligo: Symptoms, pathogenesis and treatment. Int J Immunopathol Pharmacol 2014;27:485-9.
14. Ürün M. Vitiligolu hastaların psikiyatrik muayene sonuçları. 2011.
15. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J, *et al*. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44-84.
16. Laddha NC, Dwivedi M, Mansuri MS, Gani AR, Ansarullah M, Ramachandran AV, *et al*. Vitiligo: Interplay between oxidative stress and immune system. Exp Dermatol 2013;22:245-250.
17. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: A randomized double-blind placebo-controlled study. J Eur Acad Dermatol Venereol 2007;21:942-950.
18. Jain A, Mal J, Mehndiratta V, Chander R, Patra SK. Study of oxidative stress in vitiligo. Indian J Clin Biochem 2011;26:78-81.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

Original Article

Trends of Skin Cancer Incidence in Turkey: A Hospital-Based Study

Esma Katkat Çelik[1], Leyla Baykal Selcuk[1], Şafak Ersöz[2], Deniz Aksu Arıca[1], Savaş Yaylı[1,3], Arzu Ferhatosmanoğlu[1]

[1]Department of Dermatology and Venerology, Faculty of Medicine, Karadeniz Techinical University, Trabzon, [2]Department of Pathology, Faculty of Medicine, Karadeniz Technical University, Trabzon, [3]Department of Dermatology and Venerology, Faculty of Medicine, Koç University, İstanbul, Turkey

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Abstract

Background: The incidence of skin cancers is increasing every year. The purpose of the study was to determine the change in the incidence of skin cancers and their subtypes over the years. **Materials and Methods:** A total of 1507 patients who applied to the Dermatology Clinic between January 1, 2010, and January 1, 2020, and were diagnosed with Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC), and melanoma were included in the study. Sociodemographic characteristics of the patients, comorbidities, tumor type, tumor number, lesion size, lymph node or organ metastasis, number of recurrences, and number of previous surgeries were recorded. **Results:** A total of 1056 (52.4%) patients had BCC, 733 (36.4%) SCC, and 225 (11.2%) had melanoma. The mean age was 69.8 (±14.61) in females and 67.65 (±13.33) in males ($P < 0.001$) at the time of diagnosis. The highest rate of recurrence was detected in 39 patients (7.1%) and the earliest recurrence time (15.77 months (±14.24) was detected in SCC ($P < 0.01$, $P = 0.01$, respectively). The mean age of skin cancer was found to be significantly lower in those who had undergone organ transplantation and those who had autoimmune diseases ($P = 0.004$, $P = 0.008$, respectively). Also, organ metastases were more common ($P = 0.005$), and the mean tumor size was lower in patients with autoimmune diseases ($P = 0.008$). **Conclusion:** It was found that the frequency of SCC has increased and approached BCC over the years, and the frequency of malignant melanoma has been similar. Results support that more emphasis should be placed on skin cancer screening and prevention in high-risk groups.

Keywords: Autoimmune disease, basal cell cancer, melanoma, organ transplants, squamous cell cancer

Introduction

Skin cancers have the highest global incidence among other cancer types. Although the main risk factor for all skin cancers is exposure to ultraviolet (UV) Radiation, more than 80% can be prevented.[1]

Non-melanoma skin cancers, including squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), originate from keratinocyte cells and are known as keratinocyte carcinomas.[1] BCC is a slow-growing skin tumor that rarely metastasizes, develops in sun-exposed skin,[2] and has low mortality rates. It can be locally invasive and may recur after the treatment, causing significant morbidity.

SCC, which is the second most common skin cancer after BCC, is very important in the development of cumulative sun exposure, especially in childhood and adolescence. It has been identified as an important factor for immunosuppression and tumorigenesis in recent years, including those associated with organ transplantation.[3] Also, 3.7% to 5.2% of cutaneous squamous cell carcinoma (cSCC) patients have nodal metastases and 1.5% to 2.1% die from cSCC.[4]

Melanoma, on the other hand, is among the most aggressive skin tumors known for its high mortality rate, frequent metastasis, and resistance to treatments.[5] The

Submission: 02-Oct-2023 **Revision:** 20-Dec-2023
Acceptance: 20-Dec-2023 **Web Publication:** 01-Feb-2024.

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_104_23

Address for correspondence: Dr. Arzu Ferhatosmanoğlu, Department of Dermatology and Venerology, Faculty of Medicine, Karadeniz Techinical University, Trabzon 61080, Turkey.
E-mail: arzuferhatosman@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Katkat Çelik E, Baykal Selcuk L, Ersöz S, Aksu Arıca D, Yaylı S, Ferhatosmanoğlu A. Trends of skin cancer incidence in Turkey: A hospital-based study. Turk J Dermatol 2023;17:136-43.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

incidence of cutaneous melanoma is increasing on a global scale at a faster rate each year than other types of cancer. Recent advances in systemic drug therapies in the treatment of melanoma have significantly changed patient management and outcomes, especially in advanced disease stages.[6]

The financial effects of skin cancers on healthcare costs are significant. However, the true incidence of non-melanoma skin cancers is mostly unknown because of the lower registration rates in most countries in contrast to malignant melanoma. In the present study, the purpose was to determine the general rates of skin cancers and the changes in the incidence of subtypes over the years. It was also aimed to determine the recurrence and metastasis rates according to comorbidities, gender, and clinical characteristics.

Materials and Methods

Patients who applied to the Dermatology Clinic between January 1, 2010, and January 1, 2020, and were diagnosed with SCC, BCC, and malignant melanoma clinically and histopathologically were included in the present study. The data of 2165 patients were analyzed, 658 patients were excluded because the data were missing, and a total of 1507 patients were included in the study.

Among the patients who were included in the study, 838 were diagnosed with BCC, 552 with SCC, 175 with melanoma, and 64 with more than one skin cancer. The age and year of diagnosis, gender, number of lesions, size of the lesion, diabetes, hypertension, hematological malignancy, organ transplantation, solid organ malignancy, autoimmune disease, additional diseases such as inflammatory disease, immunosuppressive drug use history, smoking, and alcohol use, family history of skin cancer, number of recurrences, lymph node or organ metastases, and number of previous surgeries of the patients included in the study were recorded from the patient files and by calling the patients by phone. The Ethics Committee Approval was obtained before starting the study.

Statistical analysis

The SPSS 23.0 statistical package program was used in the analysis of the data. The descriptive statistics of evaluation results were given as numbers and percentages, for categorical variables, mean, standard deviation (SD), and minimum (min) to maximum (max) values for the variables. The conformity of the data to the normal distribution was examined with the one-sample Kolmogorov–Smirnov test. The comparisons of the measurement data of two independent groups were made with the Mann–Whitney *U* test because the normal distribution condition was not met, and the comparisons of three or more independent groups were made with the Kruskal–Wallis test. The Chi-square test was used to analyze the differences between categorical rates and the statistical significance level was taken as $P < 0.05$.

Results

A total of 1507 patients were included in the study [896 (59.5%) males and 611 (40.5%) females]. Considering the distribution of skin cancer numbers (i.e., number of tumors) in the patients, 1056 (52.4%) had BCC, 733 (36.4%) had SCC, and 225 (11.2%) had melanoma. The mean age was 69.8 (±14.61) in women and 67.65 (±13.33) in men at the time of diagnosis. Significantly older age was detected in women ($P < 0.001$). The sociodemographic characteristics and comorbidities of the patients are summarized in Table 1 and the comparison of the rate, location, size, recurrence, and metastasis rates of skin cancer subtypes according to gender are summarized in Table 2.

The mean age at the diagnosis of skin cancer of the patients was 67.55 (±13.65) in BCC, 72.05 (±13.06) in SCC, and 64.23 (± 15) in malignant melanoma (MM), respectively. The mean age was found to be lower in melanoma patients at diagnosis ($P < 0.01$).

The highest number of recurrences was detected in 39 patients (7.1%) and the earliest recurrence time was 15.77 ± 14.24 months in SCC patients ($P < 0.01$, $P = 0.01$, respectively).

The size was found to be significantly larger in lesions in the lower extremities ($P < 0.01$).

The size of the lesions on the upper extremity and face was significantly higher in women ($P = 0.041$, $P = 0.002$). According to the mean number of surgeries, the highest mean number of surgeries was detected in BCC [1.21 (±0.44) for BCC, 1.14 (±0.37) for SCC, and 1.17 (±0.4) for MM, respectively, $P < 0.01$].

When the mean age at diagnosis of skin cancer was evaluated according to gender, BCC was similar in both genders, and SCC and MM were significantly higher in females ($P < 0.0001$, $P = 0.016$). When the mean lesion size was considered, it was found to be significantly higher in males ($P < 0.0001$). The rate of localization in the scalp and organ metastases was significantly higher in men ($P < 0.0001$, $P < 0.0001$). The mean age at diagnosis of skin cancer was 66.91 (±14.61) years in patients with lymph node metastasis, and 63.57 (±13.3) years in those with organ metastases. The mean age at diagnosis was found to be lower in patients who had lymph node and organ metastases ($P = 0.046$ and <0.0001, respectively).

Although the total incidence of skin cancer has increased in recent years, this has not been at statistically significant levels. The comparison of skin cancer subtype rates between 2010–2014 and 2015–2019 is summarized in

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Table 1: Sociodemographic characteristics and comorbidities in skin cancers

Patient variables	Total	BCC	SCC	Malignant melanoma
Gender, *n*(%)				
Female	611 (40.5)	477 (45.2)	236 (32.2)	96 (42.9)
Male	896 (59.5)	579 (54.8)	497 (67.8)	129 (57.1)
Age range, *n* (%)				
0-20	1 (0.1)	1 (0.1)	0	0
21-40	50 (3.3)	31 (2.9)	8 (1.1)	18 (8)
41-60	369 (24.5)	264 (25)	131 (17.8)	58 (25.8)
61-80	773 (51.3)	540 (51.2)	395 (53.8)	125 (55.6)
>80	314 (20.8)	220 (20.7)	199 (27.1)	24 (10.7)
Comorbidity, *n*(%)				
Hypertension	625 (41.5)	349 (41.6)	215 (43.4)	63 (36.0)
Diabetes	235 (15.6)	124 (14.8)	82 (16.6)	30 (17.1)
Solid organ malignancy	89 (5.9)	51 (6.1)	30 (6.1)	9 (5.1)
Inflammatory disease	72 (4.8)	46 (5.5)	17 (3.4)	7 (4.0)
Hematological malignancy	34 (2.3)	18 (2.1)	15(3.0)	5 (2.9)
Autoimmune disease	27 (1.8)			
Organ transplantation	11 (0.7)	6 (0.7)	6 (1.2)	0
Immunosuppressive drug, *n* (%)	80 (5.3)	42 (5%)	31 (6.3)	9 (5.1)
Smoking, *n* (%)	225 (42.5)	123 (41.7)	90 (46.9)	22 (36.1)
Alcohol use, *n* (%)	82 (17.5)	30 (15.4)	26 (44.8)	6 (10.3)
Multiple skin cancer, *n* (%)	64 (4.2)	58 (6.9)	45 (9.1)	7 (4.0)
Family history of skin cancer, *n* (%)	28 (8.9)	19 (9.9)	10 (10.0)	3 (7.7)

Table 3. The BCC rate was significantly lower in 2015–2019 (0.003), and there was no difference in the subtypes. The rate of SCC increased significantly between 2015 and 2019 ($P = 0.002$), but there was no difference in the subtypes. Although there was no increase in the rate of MM, a significant decrease was detected in the frequency of nodular MM in its subtypes between 2015 and 2019, and a significant increase in the acral MM subtype ($P < 0.0001$, $P < 0.0001$).

The comparison of age at diagnosis, tumor size, recurrence, and metastasis frequency in patients who had comorbidities is summarized in Table 4. The mean age at diagnosis of skin cancer was significantly lower in those who had organ transplantation and autoimmune disease ($P = 0.09$, $P = 0.008$). Also, organ metastases were more common ($P = 0.005$), and mean tumor size was lower in those who had autoimmune diseases ($P = 0.008$).

Discussion

In the present study, it was found that the frequency of BCC has decreased and the frequency of SCC has increased in recent years, while the frequency of MM has remained similar.

The incidence of non-melanoma skin cancer (NMSC) increased by 33% between 2007 and 2017.[7] Over the last decade, the incidence of BCC has increased by 5% annually in Europe.[8] In a retrospective study conducted with 2879 patients with NMSC (2062 BCC, 746 SCC, 71 BCC + SCC), reported from our country, BCC was reported to be the most common NMSC.[9] In a prospective study conducted by Ferhatosmanoğlu *et al.*,[10] a total of 7396 people were evaluated and skin cancer was detected in 200 patients, which constituted 2.7% of the study population. The number of SCC patients was close to the number of BCC patients. Similarly, some studies reported that the incidence of SCC is increasing, approaching that of BCC.[11] In the present study, when compared to the period between 2010–2014 and 2015–2019, it was observed that although BCC decreased, the rate of SCC increased, similar to the literature data. Contrary to our study, Kappelin *et al.*[12] reported that the incidence of BCC increased by 1.8% in Sweden. We think that as the life expectancy increases, the rate of SCC may have increased due to increased cumulative sun exposure and a relative decrease in the number of BCCs may have occurred. Although the limited duration of 5 years and the limited number of patients alone are not sufficient to show that the frequency of SCC has increased and approached the frequency of BCC, it stands out as supporting data.

Regarding gender distribution, the data from the literature on BCC indicate a higher incidence in males.[13,14] Similarly, there was male predominance in our study. The male/female ratio in patients with SCC was found to be higher in our study, similar to the literature data.[15] In the study conducted by Baykal *et al.*[16] the gender distribution of patients with melanoma was almost equal; however,

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Table 2: Comparison of rates, localization, size, recurrence and metastasis rates of skin cancer subtypes according to gender

Tumor variables	Total	Female	Male	*P* value
Age at diagnosis, skin cancer type, (mean ± SD)	68.52 (±13.9)	69.8 (±14.61)	67.65 (±13.33)	<0.001
BCC	67.55 (±13.65)	68.47 ± 14.22	68.17 ± 13.01	0.346
SCC	72.05 (±13.06)	76.53 ± 12.83	69.37 ± 12.64	**0.000**
MM	64.23 (±15)	67.60 ± 14.1	62.96 ± 14.9	**0.016**
BCC types				0.055
Nodular	706 (67)	311 (67.6)	395 (66.5)	
Cystic	130 (12.3)	29 (6.3)	31 (5.2)	
Pigmented	94 (8.9)	28 (6.1)	36 (0.1)	
Morphea-like	64 (6.1)	49 (10.7)	45 (7.6)	
Superficial	60 (5.7)	43 (19.3)	87 (14.6)	
SCC types				0.233
Well -differentiated	498 (67.8)	336 (67.5)	170 (72)	
Poorly differentiated	236 (32.2)	162 (32.5)	66 (28)	
Melanoma types				0.899
Nodular	117 (52)	50 (51.5)	67 (52.3)	
Superficial spreading	57(25.3)	16(16.5)	19(14.8)	
Lentigo MM	35(15.6)	8(8.2)	8(6.2)	
Acral Lentiginous	16(7.1)	23(23.7)	34(26.6)	
Residential area				**<0.0001**
Face	1472 (73.1)	616 (78.6)	856 (69.6)	
Scalp	137 (6.8)	24 (3.1)	113 (9.2)	**<0.0001**
Neck	39 (1.9)	12 (1.5)	27 (2.2)	
Upper extremity	90 (4.5)	35 (4.5)	55 (4.5)	
Lower extremity	171 (8.5)	66 (8.5)	105 (8.5)	
Body	88 (4.4)	24 (3.1)	64 (5.2)	
Nail	4 (0.2)	1 (0.1)	3 (0.2)	
Genitalia	8 (0.4)	2 (0.3)	6 (0.5)	
Localization, Mean size(±SD)				
Lower extremity	3.47 (±2.92)	3.92 ± 4.03	4.18 ± 4.67	0.863
Neck	2.31 (±2.03)	2.22 ± 1.79	2.50 ± 2.57	0.694
Scalp	2.21 (±2.26)	1.99 ± 1.89	3.27 ± 3.46	0.113
Upper extremity	2.08 (±1.75)	2.42 ± 2.03	1.55 ± 0.99	**0.041**
Body	1.97 (±1.56)	2.03 ± 1.55	1.80 ± 1.60	0.346
Face	1.36 (±1.26)	1.42 ± 1.27	1.28 ± 1.23	**0.002**
Neck	2.31 (±2.03)	2.22 ± 1.79	2.50 ± 2.57	0.694
Number of recurrences *n*(%)		27 (4.4)	46 (5.1)	0.608
Melanoma		13 (7.4)	8 (8.3)	6 (4.7)
SCC		39 (7.1)	20 (4.4)	10 (5.2)
BCC		34 (4.1)	19 (3.2)	11(2.4)
Time to recurrence (mean ± SD)		19.11 (±16.72)	23.29 (±23.4)	0.752
BCC	29.06 (±26.14)	27.64 ± 22.07	35.74 ± 33.12	0.703
Melanoma	18.62 (±15.3)	24.33 ± 18.60	15.00 ± 11.34	0.310
SCC	15.77 (±14.24)	10.20 ± 7.81	15.12 ± 12.14	0.445
Number of recurrences (Mean ± SD)		1.27 (±0.75)	1.38 (±1.22)	0.634
Lesion size, (mean ± SD)	1.69 ± 1.89	1.61 (±1.93)	1.75 (±1.86)	**<0.0001**
LN met, *n* (%)	164 (8.1)	57 (7.3)	107 (8.7)	0.253
Organ met, *n* (%)	119 (5.9)	25 (3.2)	94 (7.6)	**<0.0001**

P values below 0.05 are considered statistically significant. Significant *p* values are colored in bold

there was male predominance in our study. This may be associated with the fact that men spend more time outside in our country, including childhood periods, and their clothing choices and exposure of more body surface area to the sun's rays.

The mean age at diagnosis in patients with melanoma was found to be lower than in other skin cancers in the present study. Age at diagnosis of skin cancer in women was older in the MM and SCC groups and it was close to the age of diagnosis in male BCC patients. No significant gender

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Table 3: The comparison of skin cancer subtype rates between 2010-2014 and 2015-2019

Skin cancer characteristics	2010–2014	2015–2019	*P* value
Age mean, mean ± SD	68.91 ± 12.64	69.48 ± 14.56	0.072
Gender *n*(%)			0.143
Female	350 (37.2)	434 (40.4)	
Male	591 (62.8)	639 (59.6)	
BCC *n*(%)	527 (56)	529 (49.3)	**0.003**
Subtype *n*(%)			0.294
Nodule	344 (65.4)	362 (68.6)	
Cystic	36 (6.8)	24 (4.5)	
Pigmented	34 (6.5)	30 (5.7)	
Morphea	42 (8)	52 (9.8)	
Superficial	70 (3.3)	60 (11.4)	
SCC *n*(%)	309 (32.8)	424 (39.5)	**0.002**
Subtype			
Well-differentiated	189 (68.2)	226 (60.4)	0.105
Poorly differentiated	89 (31.8)	147 (39.6)	
MM *n*(%)	105 (11.2)	120 (11.2)	1.000
Subtype			**<0.0001**
Superficial	14 (13.5)	21 (17.4)	
Nodule	73 (70.2)	44 (36.4)	**<0.0001**
Acral	10 (9.6)	47 (38.8)	**<0.0001**
LMM	7 (6.7)	9 (7.4)	

P values below 0.05 are considered statistically significant. Significant *p* values are colored in bold

Table 4: Comparison of age at diagnosis, tumor size, recurrence, and metastasis frequency in patients with comorbidities

Skin cancer characteristics	HM	*P* value	SOM	*P* value	OT	*P* value	ID	*P* value	AD	*P* value
Age at diagnosis, mean ± SD	70.24 (±11.51)	0.743	69.24 (±10.83)	0.130	59.09 (±11.59)	**0.004**	69.21 ± 13.07	0.181	63.11 ± 12.96	**0.008**
Multiple skin cancer *n* (%)	4 (11.8)	0.053	4 (4.5)	0.788	1 (9.1)	0.381	1 (1.4)	0.363	2 (7.4)	0.319
Number of recurrences *n* (%)	2 (5.9)	0.679	6 (6.7)	0.439	0	1.000	2 (%2.3)	0.579	3 (8.1)	0.175
Organ met, *n* (%)	6 (11.3)	0.127	9 (6.1)	0.856	0	1.000	1 (1.1)	0.059	7 (18.9)	**0.005**
LN met, *n* (%)	4 (7.5)	1.000	11 (7.5)	0.876	0	0.621	3 (3.4)	0.111	0	0.069
Lesion size, mean ± SD	1.42 ± 1.35	0.206	1.47 ± 1.41	0.472	1.14 ± 1.70	0.383	1.50 ± 1.28	0.987	1.11 ± 1.28	**0.008**

HM = Hematological malignancy, SOM = Solid organ malignancy, OT = Organ transplantation, ID = Inflammatory disease, AD = Autoimmune disease, LN met = lymphe node metastasis

P values below 0.05 are considered statistically significant. Significant *p* values are colored in bold

differences were detected in BCC, SCC, and MM subtypes. Similar results were obtained by Ciążyńska *et al*. (the mean age for BCC was similar in males and females, while the mean age at diagnosis was older in SCC in women than in men.[17] In a study evaluating NMSCs, the mean age at diagnosis was 63.4 (±15.3) in BCCs and 70.5 (±13.4) in SCCs, and similar to our study, it was higher in patients with SCC than in patients with BCC.[15] In a study that was published in 2016, the mean age of BCC was found to be 68.83 years, similar to our study.[18] In the study of Baykal *et al*.[16] the mean age of patients diagnosed with melanoma was found to be lower than in our study (64.23 vs. 57.7 ± 19.7). In the study conducted by Azarjana *et al*.[19] the mean age at diagnosis of melanoma patients was reported as 61.3 (±15.3), 60.7 (14.7) in men, and 61.6 (±15.6) in women. In our study, the mean age at diagnosis of melanoma patients and the age at diagnosis was higher in both men and women. We believe that this may be associated with the delayed first application in our region. The belief that "if the knife touches, cancer will occur" is an important factor in the late admission of patients in our country.

Although it is reported in the literature that the most common skin cancer is SCC in immunosuppressed

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

patients,[20] BCC was the most common skin cancer in immunosuppressed patients in this study.

In a study in the literature, 2.6% of the patients who had BCC were found to be immunosuppressive, 35.2% of immunosuppressive cases had organ transplantation, and 55.7% had inflammatory disease.[15] In our study, although the rate of immunosuppression was higher in patients with BCC (14.5%), organ transplantation (5%), and inflammatory disease (38%) were observed less frequently as the cause of immunosuppression. High immunosuppressive status was associated with the fact that our clinic was located in a comprehensive university hospital and our consultation rates were high.

A total of 4.8% of the SCC patients were found to be immunosuppressive in the same study. Organ transplantation was present in 33.8% of immunosuppressive cases, inflammatory disease in 42.5%, and hematological malignancy in 2.5%.[15] In our study, immunosuppression rate (12.3%), and hematological malignancy (22%) were found to be higher in SCC patients, and organ transplantation rate (8.8%), and inflammatory disease (25%) were observed less frequently. In a study that evaluated patients with SCC, Actinic Keratosis, and Bowen's diagnosis, 10.3% of the patients had a history of taking immunosuppressive drugs. This rate was lower (6.3%) in our study.[21]

In the study of Barazzetti *et al*.[22] conducted with SCC patients, the most common comorbid condition was found to be hypertension, and the second most frequent was diabetes, similar to our study. High rates may be associated with a higher expected age of onset of SCC.

In a study that was conducted in our country, smoking history and alcohol use were found to be risk factors for BCC and SCC, and smoking history was found to be a risk factor for MM.[10] In another study, 45.6% of BCCs and 53.6% of SCCs had a history of smoking.[15] Approximately, half of SCC patients used cigarettes (54.3%) and alcohol (43.5%) in another study.[22] In our study, smoking rates were similar to the literature data, and alcohol use rates were found to be lower than in the literature. It is considered that this may be caused by social–cultural differences.

When the average of recurrence times was evaluated, the earliest recurrence was detected in SCC and the latest recurrence in BCC. The lesion size was found to be significantly larger in lesions in the lower extremities. It is considered that lower extremity lesions can be neglected more by patients than facial lesions and may delay the referral to a doctor. According to the average number of surgeries, the highest mean number of surgeries was found in BCC.

In the present study, the recurrence rate was found to be 4.1% in BCC and 7.1% in SCC. Similar to this study, the overall BCC recurrence rate in the 1062 patient cohort study was reported as 4%.[23] Recurrence rates varying between 4.6% and 6.7% are reported in the literature for cSCC.[24] The recurrence rate in terms of SCC was found to be higher in the present study than in the literature. This may be related to our higher number of immunosuppressive cases when compared to other studies.

In another prospective cohort study, the overall tumor recurrence rate was reported as 3.5% in NMSC, which was quite low compared to our study.[25] This may be because of the different surgical methods employed.

There were also differences between sexes regarding tumor sites. The head and neck region was the prominent site of NMSC, this is in line with the literature.[26] In the present study, the rate of skin cancer on the scalp was found to be higher in men than in women. This may be because of direct sunlight exposure to the balding skin as a result of baldness with Androgenic Alopecia, which increases with age in men.

In the study conducted by Muzic *et al*.[15] the mean size of BCC lesions was found to be 1.0 (±0.6) cm, and that of SCC lesions was 1.1 (±0.6) cm. In the study of Ma *et al*.[27] the tumor size of melanoma patients was reported to be ≤6 mm in 20.6%, 7-12 mm in 34.2%, 13-30 mm in 32.6%, 31-42 mm in 4%, and >42 mm in 8.6%. In the present study, more advanced lesions were detected in all skin cancer types compared to the literature data. This may be because of the low level of awareness of society in terms of skin cancer.

In a study evaluating the distribution of histopathological types of skin cancers, histopathological types of BCC were found to be 43.9% nodular, 17.1% superficial, 5.9% infiltrative, and 1.6% morphea-like.[15] A higher percentage of nodular subtypes was detected in men (66.5%) and a higher rate of superficial BCC in women (28.2%).[15] In another study, nodular and morpheiform BCC occurred more frequently in women (male/female ratio 0.96, M/F ratio 0.73).[28] In this study, a higher rate of superficial BCC was detected in women, although not at a statistically significant level. More comprehensive studies are needed to uncover the relationship between BCC subtypes and gender distribution. In the same study, the majority of BCCs (83.1%) were found to be localized in the head region, as in the present study.[28]

Also, no significant gender difference was detected in the present study between poorly differentiated and well-differentiated SCC cases and MM subtypes.

It is already known that autoimmune diseases are associated with an increased risk of melanoma and NMSC.[29,30] The reason for the significantly lower mean age at diagnosis of skin cancer in patients with autoimmune diseases or organ transplantation in our study may be

the chronic inflammatory involvement of the skin or immune-modulating treatments targeting autoimmune conditions. Larger studies are needed to explain the fact that the tumor size is significantly lower in patients with autoimmune diseases, while the organ metastasis rate is significantly higher.

Conclusion

The change in the incidence of melanoma and NMSCs and their subtypes over the years has been revealed in the present study. The increased frequency of SCC between 2015 and 2019 compared to the previous 5-year period and approaching BCC supports the recent literature. Unfortunately, studies reporting the effects of gender and comorbidities on recurrence and metastasis in skin cancers are limited. In the present study, when all skin cancers were evaluated, the rate of localization on the scalp, the size of the lesion, and the rate of organ metastasis were found to be significantly higher in men, which contributes to the literature on "skin cancers-gender relationship." In the present study, the mean age at diagnosis of skin cancer was also found to be significantly lower in those with organ transplantation and those with autoimmune diseases. Also, organ metastases were more common in patients who had autoimmune diseases and the mean tumor size was lower. We think supporting the findings with a larger series of studies will make an additional contribution to the management of skin cancers.

Data availability statement

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

Author contributions

Conception or design of the work: EKÇ, AF, and LBS. Data collection: EKÇ, AF, LBS, ŞE, DAA, and SY. Data analysis and interpretation: EKÇ, AF, and LBS. Critical revision of the article: EKÇ, AF, LBS, and DAA. Final approval of the version to be published: EKÇ, AF, and LBS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Jones OT, Ranmuthu CK, Hall PN, Funston G, Walter FM. Recognising skin cancer in primary care. Adv Ther 2020;37:603-16.
2. Basset-Seguin N, Herms F. Update on the management of basal cell carcinoma. Acta Derm Venereol 2020:100:adv00140.
3. Alam M, Armstrong A, Baum C, Bordeaux JS, Brown M, Busam KJ, *et al*. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-78.
4. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: A systematic review and meta-analysis. JAMA Dermatol 2016;152:419-28.
5. Kim JE, Chung BY, Sim CY, Park AY, Lee JS, Whang KU, *et al*. Clinicopathologic features and prognostic factors of primary cutaneous melanoma: A multicenter study in Korea. J Korean Med Sci 2019;34:e126.
6. Hyams DM, Cook RW, Buzaid AC. Identification of risk in cutaneous melanoma patients: Prognostic and predictive markers. J Surg Oncol 2019;119:175-86.
7. Hall ET, Fernandez-Lopez E, Silk AW, Dummer R, Bhatia S. Immunologic characteristics of nonmelanoma skin cancers: Implications for immunotherapy. Am Soc Clin Oncol Educ Book 2020;40:1-10.
8. Dika E, Scarfì F, Ferracin M, Broseghini E, Marcelli E, Bortolani B, *et al*. Basal cell carcinoma: A comprehensive review. Int J Mol Sci 2020;21:5572-5572.
9. Ceylan C, Oztürk G, Alper S. Non-melanoma skin cancers between the years of 1990 and 1999 in Izmir, Turkey: Demographic and clinicopathological characteristics. J Dermatol 2003;30:123-31.
10. Ferhatosmanoğlu A, Selcuk LB, Arıca DA, Ersöz S, Yaylı S. Frequency of skin cancer and evaluation of risk factors: A hospital-based study from Turkey. J Cosmet Dermatol 2022;21:6920-27.
11. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol 2018;78:237-47.
12. Kappelin J, Green AC, Ingvar A, Ahnlide I, Nielsen K. Incidenceandtrends of basalcellcarcinoma in Sweden: A population-basedregistrystudy. Br J Dermatol 2022;186:963-9.
13. Kasumagic-Halilovic E, Hasic M, Ovcina-Kurtovic N. A clinical study of basal cell carcinoma. Med Arch 2019;73:394-8.
14. Fania L, Didona D, Morese R, Campana I, Coco V, Di Pietro FR, *et al*. Basal cell carcinoma: From pathophysiology to novel therapeutic approaches. Biomedicines 2020;8:449.
15. Muzic JG, Schmitt AR, Wright AC, Alniemi DT, Zubair AS, Lourido JMO, *et al*. Incidence and trends of basal cell carcinoma and cutaneous squamous cell carcinoma: a population-based study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clin Proc 2017;92:890-8.
16. Baykal C, Atci T, Polat Ekinci A, Buyukbabani N. An update on cutaneous melanoma in Turkey: Evaluation of 19-year data in a single tertiary centre and review of the literature. J Eur Acad Dermatol Venereol 2017;31:236-40.
17. Ciążyńska M, Kamińska-Winciorek G, Lange D, Lewandowski B, Reich A, Sławińska M, *et al*. The incidence and clinical analysis of non-melanoma skin cancer. Sci Rep 2021;11:4337-4337.
18. Luz FB, Ferron C, Cardoso GP. Analysis of effectiveness of a surgical treatment algorithm for basal cell carcinoma. An Bras Dermatol 2016;91:726-31.
19. Azarjana K, Ozola A, Ruklisa D, Cema I, Rivosh A, Azaryan A, *et al*. Melanoma epidemiology, prognosis and trends in Latvia. J Eur Acad Dermatol Venereol 2013;27:1352-9.
20. Brin L, Zubair AS, Brewer JD. Optimal management of skin cancer in immunosuppressed patients. Am J Clin Dermatol 2014;15:339-56.
21. Schmitt J, Haufe E, Trautmann F, Schulze HJ, Elsner P, Drexler H, *et al*; FB- 181 Study Group. Is ultraviolet exposure acquired at work the most important risk factor for cutaneous squamous cell carcinoma? Results of the population- based case–control study FB-181. Br J Dermatol 2018;178:462-72.
22. Barazzetti DO, Barazzetti PHO, Cavalheiro BT, Ely JB, Nunes DH, de Faria Stamm AMN. Quality of life and clinical and demographic characteristics of patients with cutaneous squamous cell carcinoma submitted to tumor resection by double-bladed scalpel. An Bras Dermatol 2019;94:304-12.
23. Kyrgidis A, Vahtsevanos K, Tzellos TG, Xirou P, Kitikidou K, Antoniades K, *et al*. Clinical, histological and demographic predictors for recurrence and second primary tumours of head and neck basal cell carcinoma A 1062 patient-cohort study from a tertiary cancer referral hospital. Eur J Dermatol 2010;20:276-82.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

24. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma A 10-year, single-institution cohort study. JAMA Dermatol 2013;149:541-7.
25. Chren M, Torres JS, Stuart SE, Bertenthal D, Labrador RJ, Boscardin WJ. Recurrence after treatment of nonmelanoma skin cancer: A prospective cohort study. Arch Dermatol 2011;147:540-6.
26. Kansara S, Bell D, Weber R. Surgical management of non melanoma skin cancer of the head and neck. Oral Oncol 2020;100:104485.
27. Ma Q, Suo H, Zhu L, Qian Y, Sun X, Xie J, *et al*. Prognostic significance of tumor size for primary invasive cutaneous melanoma: A population-based study, 2004-2016. Cancer Med. 2020;9:4561-71.
28. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002;147:41-7.
29. Ehrenfeld M. Autoimmune diseases and cancer. In: Anaya, J.M., Shoenfeld, Y., Rojas-Villarraga, A., *et al*., editors. Autoimmunity: From Bench to Bedside. Bogota (Colombia): El Rosario University Press; 2013.
30. Raaschou P, Simard JF, Holmqvist M, Askling J; ARTIS Study Group. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. BMJ 2013;346:f1939.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 03/06/2024

Original Article

Association between Serum Zinc Levels and Multiple Cutaneous Warts: A Cross-Sectional Study

Divya Mani, Jude Ernest Dileep, Damayandhi Kaliyaperumal, Sheela Kuruvila, Jagadeeshkumar Govardhan[1], Ilakkiapriya Sadasivam, Rajkiran Takharya[2]

Department of DVL, Aarupadai Veedu Medical College and Hospital, Puducherry, [1]Department of DVL, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India, [2]Department of DVL, Manipal Tata Medical College, Jamshedpur, Jharkhand, India

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Abstract

Background: Warts are cutaneous manifestations of human papillomavirus (HPV). Trauma and maceration facilitate initial epidermal inoculation. The spread may then occur by autoinoculation. Local and systemic immune factors appear to influence the spread. Zinc is an essential micronutrient having a wide spectrum of actions. Deficiency of the same adversely affects the immune function, especially, T cell functions. The role of zinc as an immunological modulator activates lymphocytes and cytokines against the penetration and replication of viruses, which has increasingly been recognized. Numerous skin disorders have been linked to zinc deficiency. A high dose of oral zinc sulfate has shown outstanding therapeutic efficacy and prevents relapse in patients with recalcitrant and multiple warts. Owing to the therapeutic efficacy of oral zinc in the treatment of warts, the current study was undertaken to find out the association between serum zinc level and multiple cutaneous warts among the study population. **Materials and methods:** One hundred and ten patients with cutaneous warts met the inclusion criteria and an equal number of age and sex-matched controls were enrolled. A consecutive sampling technique was used for the enrolment. Details regarding the duration, number, clinical type, size, and distribution of the warts were recorded. Serum zinc levels were estimated in both cases and controls. Data were tabulated and analyzed using the SPSS software version 20. **Results:** The reference range for normal serum zinc levels was taken as 60–180 µg/dL. Normal serum zinc levels were found in 91 (100%) of the cases and 100 (110%) of the controls; high levels were found only in 9 (10%) of the cases. Cases were found to have significantly higher mean serum zinc levels compared with the controls. (121.1 ± 35.78 µg/dL vs. 101.8 ± 20.48µg/dL, $P = 0.0001$). **Conclusion:** Patients with multiple cutaneous warts were found to have higher mean serum zinc levels compared with age and sex-matched controls. There was no significant association of serum zinc levels with the duration or the number of warts.

Keywords: Cutaneous, warts, HPV, zinc

Introduction

Warts are cutaneous manifestations of human papillomavirus (HPV). Common warts, plantar warts, flat or planar warts, and genital warts are some of the clinical manifestations of HPV infection.[1] There are over 100 HPV subtypes.[2] Trauma and maceration facilitate the initial epidermal inoculation. The spread may then occur by autoinoculation.[3] Local and systemic immune factors appear to influence the spread; the immunosuppressed patients are at particular risk of developing generalized lesions that are difficult to treat.[4] Humoral immunity provides resistance to HPV infection; the cellular immunity helps the established infection to regress.[5]

A variety of therapeutic interventions are available. The common approaches include chemical or physical destruction of the affected tissue, enhancement of the local immune response, and antiproliferative therapy.[6,7]

Submission: 10-Sep-2023 **Revision:** 12-Nov-2023
Acceptance: 22-Dec-2023 **Web Publication:** 01-Feb-2024.

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_94_23

Address for correspondence: Dr. Damayandhi Kaliyaperumal, Department of DVL, Aarupadai Veedu Medical College and Hospital, Pondy Cuddalore Main Road, Kirumampakkam, Bahour Commune Panchayat, Puducherry 607402, India.
E-mail: deepakaliyaperumal@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Mani D, Dileep JE, Kaliyaperumal D, Kuruvila S, Govardhan J. Sadasivam I, *et al.* Association between serum zinc levels and multiple cutaneous warts: A cross-sectional study. Turk J Dermatol 2023;17:144-51.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Zinc is an essential micronutrient having a wide spectrum of actions. The zinc deficiency adversely affects the immune function, especially, T cell functions.[8] Zinc as an immunological modulator, activates lymphocytes, releasing cytokines against the penetration, and replication of the viruses.[9] A high dose of oral zinc sulfate has shown outstanding therapeutic efficacy and prevents relapse in patients with recalcitrant multiple warts.[10] Owing to the therapeutic efficacy of oral zinc in the treatment of warts, the current study was undertaken to find out the association between the serum zinc level and multiple cutaneous warts among the study population.

Materials and Methods

This comparative study was conducted in the Department of Dermatology of a tertiary care teaching hospital in South India, from December 2020 to June 2022. Patients with a clinical diagnosis of multiple cutaneous warts were included in this study. The duration of the disease, number, types of warts, size, and distribution of the warts were noted.

All patients aged 10–56 years with multiple (more than three) cutaneous viral warts attending the Dermatology Outpatient Department, without any other dermatological diseases were included in study. Patients who were not willing to participate in the study, patients who were on zinc supplementation or any immunosuppressive therapies, and those with chronic diarrhea and acrodermatitis were excluded.

One hundred and ten patients with cutaneous viral warts meeting the inclusion criteria were enrolled. The consecutive sampling technique was used. The same number of healthy individuals were taken as controls after matching with the age and sex. An informed written consent was taken from the patients. Venous blood sample from each control and study participant was taken for the zinc level assessment. The serum zinc level estimation was done by Nitro-2-(5-Nitro-2-pyridylazo)-5-(N-propyl-3-sulfopropylamino) Phenol disodium salt, dihydrate methods using Sigma–Aldrich Kit (Bangalore). The normal range of serum zinc level was considered to be 60–180 μg/dL.

The data were fed in Microsoft Excel and analyzed by the Statistical Package for Social Service (SPSS)-version 20, IBM (Chicago, IL,USA). Descriptive data were expressed in mean ± standard deviation along with the frequency table. The mean of continuous variables was compared using the two-tailed independent Student *t* test, and qualitative variables were compared using chi-square test. The correlations were computed by Pearson's correlation coefficient. *P* value of ≤0.05 was considered to be statistically significant.



Figure 1: Multiple warts over the face



Figure 2: Verruca vulgaris over the dorsum of left foot

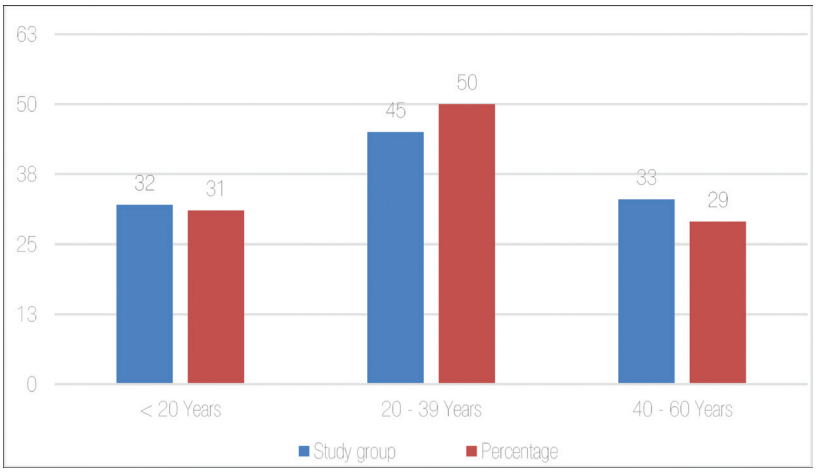
Results

The study consisted of two groups, among which 110 were cases with multiple cutaneous warts, and 110 were healthy controls. More number of participants belonged to the age group of 20–39 years in both, cases 45 (41%) and control 50 (45.5%) groups. The mean age of the cases was 31.41 years, and controls was 31.57 years. Males were 66 (60%), and females were 44 (40%) among the cases. Regarding the duration of warts, 79 (72%) cases had warts for <12 months duration, followed by 25 (22%) who had warts for 1–2 years and 6 (6%) for >3 years. Fifty (46%) cases had 4 warts followed by 39 (35%) who had 5–10 warts and 21 (19%) who had >10 warts. A more common type of wart is verruca vulgaris observed in 38 (34.5%) cases, followed by palmar wart in 20 (18%) cases and filiform warts in 15 (13%) cases [Figures 1 and 2]. More than two types of warts were observed in 37 (33.6%) cases [Table 1]. We observed that 37 (34%) of the warts were present on the right and left hand followed by 9 (8%) on the face and 6 (5%) on the neck. We also observed a few warts on the lips,

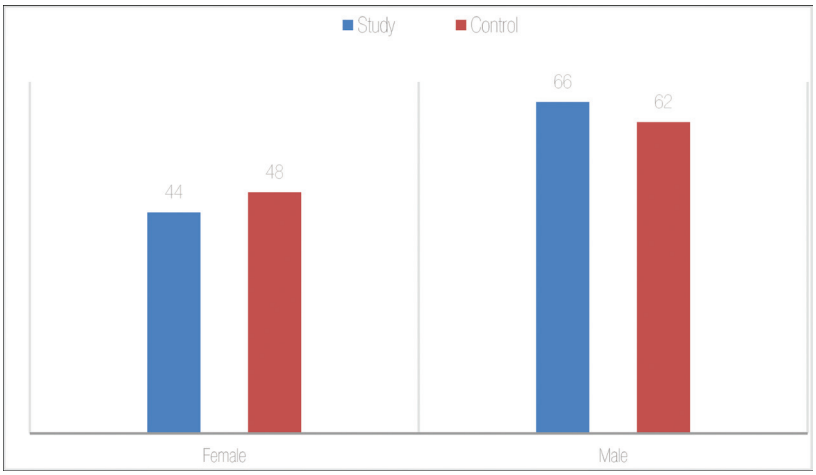
Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Table 1: Distribution of patient's demographics and clinical features

Variables	Study group	Control group	*P* value
Age group (years)			
<20	32 (29%)	31 (30%)	0.764
20–39	45 (41%)	50 (45.5%)	
40–60	43 (30%)	29 (24.50%)	
Mean ± SD	31.41 ± 14.30	31.57 ± 13.90	
Gender			
Male	44 (40%)	48 (44%)	0.584
Female	66 (60%)	62 (56%)	
Duration of warts			
<12 months	79 (72%)	NA	NA
1–2 years	25 (22%)		
3–4 years	3 (3%)		
> 4 years	3 (3%)		
Number of warts			
<4	50 (46%)	NA	NA
5–10	39 (35%)		
>10	21 (19%)		
Types of warts			
Filiform warts	15 (13%)	NA	NA
Palmar warts	20 (18%)		
Verruca vulgaris	38 (35%)		
More than two types of warts	37 (34%)		



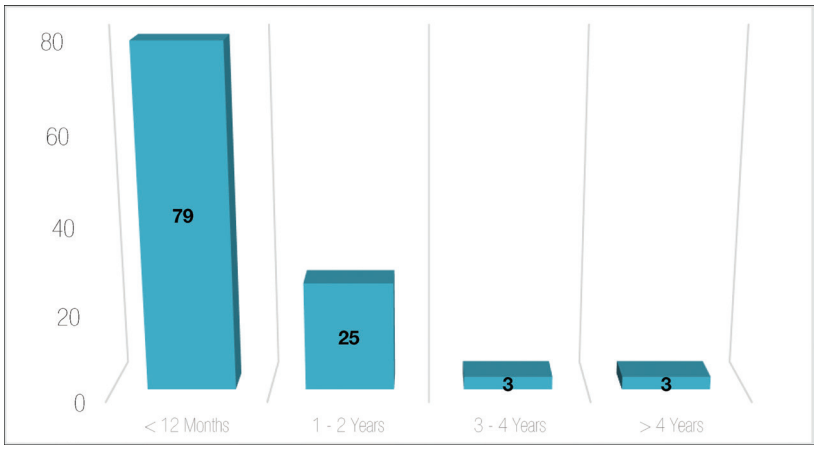
Bar diagram representing the distribution of age among study and control groups.



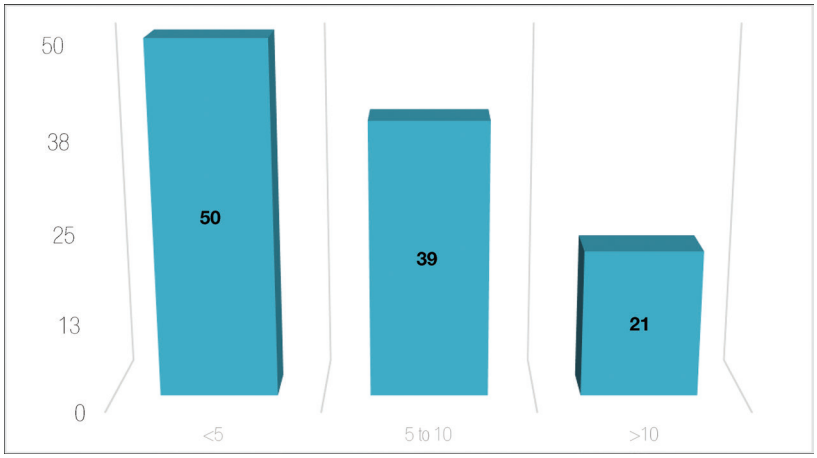
Bar chart representing the distribution of gender among study and control groups.

Table 1. Continued

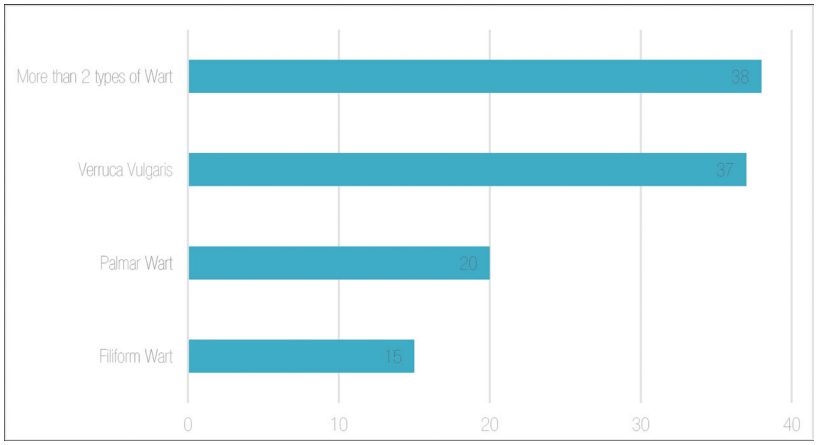
Variables	Study group	Control group	*P* value



Bar diagram representing the distribution of duration of warts among study participants.



Bar diagram representing the distribution of number of warts among study participants.



Bar diagram representing the distribution of types of warts among study participants.

NA = not applicable, SD = standard deviation

nose, eyelids, neck, scalp, and arms. Warts were present in more than two sites in 43% of the cases.

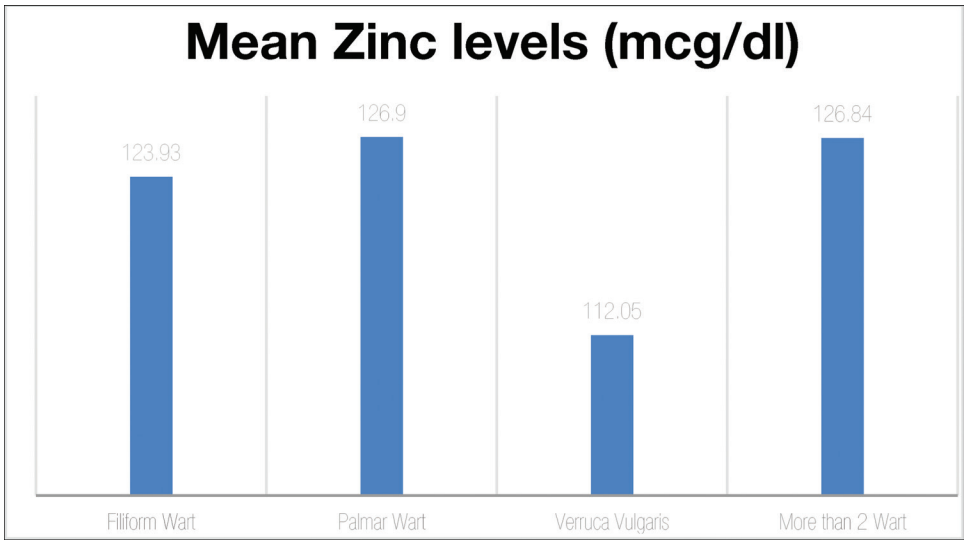
From the current study, we observed that there is no significant difference in serum zinc levels among different types of warts ($P = 0.176$) and different numbers of warts [Table 2]. In this study, the normal serum zinc reference range was taken as 60–180 µg/dL. Normal levels were observed in 100 (91%) of the study participants and 110 (100%) in the control group; high levels were observed in 10 (9%) of the study participants in the case group [Table 3].

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Table 2: Statistical comparison of serum zinc level between different types of warts

Type of warts	Zinc levels (μg/dL)	95% confidence interval for mean		Minimum	Maximum	*P* value
		Lower bound	Upper bound			
Filiform wart	123.93 ± 29.03	107.85	140.01	85	185	
Palmar wart	129.10 ± 40.925	109.95	148.25	73	219	0.176 (NS)
Verruca vulgaris	111.39 ± 31.59	101.01	121.78	68	265	
More than two warts	125.65 ± 38.45	112.83	138.47	81	216	
Total	121.12 ± 35.78	114.36	127.88	68	265	

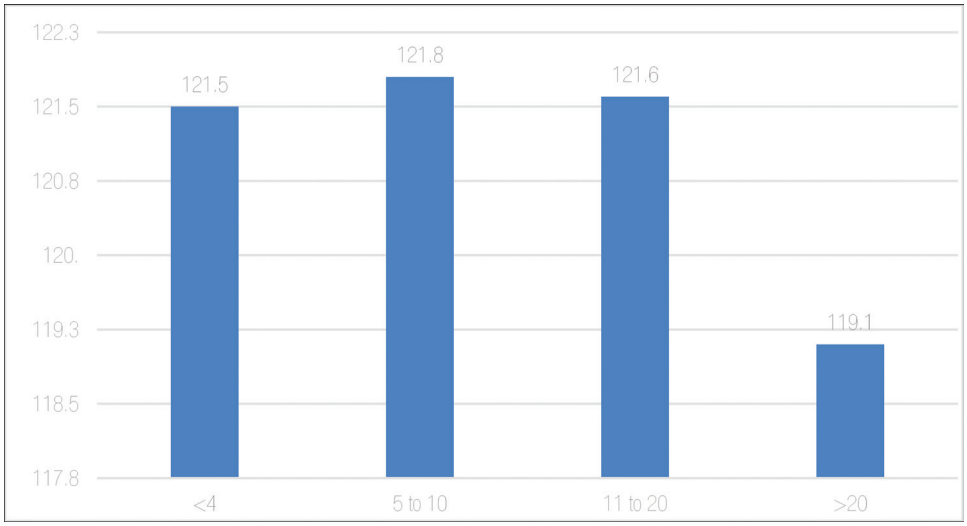


Statistical comparison of Serum Zinc Level between different types of warts.

NS, not significant

Table 3: Statistical correlation of zinc level with different numbers of warts

Number of warts and parameters	Minimum	Maximum	Mean	Standard deviation	*P* value
<4	68.00	265.0	121.5	41.53	0.9978 (NS)
5–10	81.00	216.0	121.8	31.71	
11–20	89.00	219.0	121.6	36.77	
>20	81.00	141.0	119.1	19.92	

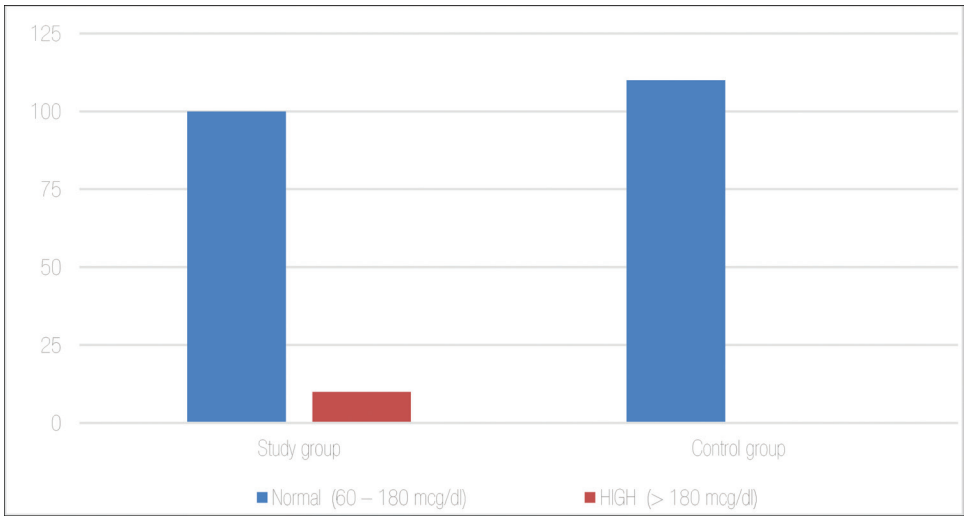


Statistical correlation of Zinc levels with different numbers of warts

NS, not significant

Table 4: Comparison of serum zinc level between the groups

Serum zinc level	Study group	Control group	*P* value
60–180 µg/dL (normal)	100 (91%)	110 (100%)	**0.001**
>180 µg/dL (high level)	10 (9%)	0	
Mean ± SD	121.1 ± 35.78	101.8 ± 20.48	



Bar diagram representing the distribution of serum zinc levels among study and control groups

SD, standard deviation; Bold value represents ***P*< 0.05**

The mean zinc level of the study group was 121.1 ± 35.78 µg/dL, and the control group was 101.8 ± 20.48 µg/dL, which was significantly higher in the study group [Table 4].

Discussion

Warts are benign lesions that occur in the mucosa and skin.[11] Warts are caused by the HPV, with over 100 types of HPV identified. HPV may occur at any site. The primary manifestations of HPV infection include common warts, genital warts, flat warts, deep palmoplantar warts (*Myrmecia*), focal epithelial hyperplasia, epidermodysplasia verruciformis, and plantar cysts. Warts may be transmitted by direct or indirect contact. Events that disrupt the normal epithelial barrier increase the likelihood of developing warts. Warts often resolve spontaneously within a few years. Some high-risk HPV subtypes are associated with malignancies. Based on their association with cervical cancer and precursor lesions, HPVs can also be grouped into high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. Included in the high-risk group are some HPV types that are less frequently found in cancers but are often found in squamous intraepithelial lesions. HPV types 5, 8, 20, and 47 have oncogenic potential leading to epidermodysplasia verruciformis.

Acanthosis, digitated epidermal hyperplasia, papillomatosis, compact orthokeratosis, hypergranulosis, tortuous capillaries inside the dermal papillae, and vertical tiers of parakeratotic cells with red blood cells entrapped above the ends of the digitations are the histopathologic characteristics.

The treatment options include chemical agents (salicylic acid, lactic acid, monochloroacetic, bichloroacetic acids, trichloroacetic acid, formalin, and glutaraldehyde), antimitotic agents (5-fluorouracil, bleomycin, and podophyllin resin podophyllotoxin), cryotherapy, surgery, immunotherapies (cimetidine, interferon, diphencyprone, oral zinc supplementation, levamizole, and intralesional purified protein derivative/vitamin D3/measles, mumps, rubella/bacille calmette-guerin/trichophytin).

In our study, we observed that males (60%) were more in number compared with females (40%). Our study also reported that a greater number of participants belong to the age group of 20–39 years (41%), the mean age of the study group was 31.41 years, and the control group was 31.57 years. Sixty percent of the study group participants were male, and 40% were female. A greater number of participants belonged to the age group of 20–39 years in both study (41%) and control (45.5%) groups.

In a similar study done by Luong *et al.*[11] estimating serum zinc level in 78 patients with multiple warts, 41 were males and 37 were females, and the mean age of the study group was 32.37 years. Another similar study was done by Raza *et al.*[12] reported the age of the patients ranged from 12 to 65 years, and the mean age of the study group was 25.88 + 8.90 years, and the majority of the patients were in the age group of 21–30 years (n = 30, 40%). Out of

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

75 patients, 52 (69.3%) were males, and 23 (30.7%) were females. In a study done by Ranjit *et al*.,[13] the frequency of distribution of cutaneous viral warts was more among the males (54%) compared with females (46%), in accordance with our findings. The male predominance noted in the present study could be because of a greater likelihood of occupational trauma and environmental exposure among men.

In this study, we observed 72% of the patients were having warts for <12 months duration, 22% of the cases were having warts for 1–2 years duration, 6% of the cases were having warts for more than years, and 46% of the cases were having <5 warts followed by 5–10 warts (35%) and >10 warts (19%). A study done by Naseri *et al*.[14] observed most of the patients had ≥20 warts on the body surface, half of them were located on the upper extremities, and the duration of disease was less than 1 year in 70% of patients and more than 2 years in 16.7% of them.

In the current study, the most common type of wart we observed was verruca vulgaris in 35% followed by palmar wart in 18% and filiform wart in 13% of the participants. More than two types of warts were observed in 34% of the participants.

In our study, the normal serum zinc reference range was 60–80 μg/dL, normal level was observed in 91% of the cases, and a high level was observed in 9% of the cases. The mean serum zinc level was 121.43 ± 35.78 μg/dL in cases, which was significantly higher than that of controls. No cases were seen with decreased serum zinc levels in our study. We also observed that there was no significant difference in serum zinc levels among different types of warts (P = 0.176), also there was no significant difference in zinc level among the number of warts.

In contrast to our finding, many studies have reported decreased serum zinc levels in patients with multiple cutaneous warts. In a study done by Luong *et al*.,[11] the serum zinc level in patients with genital warts had a mean ± SD value of 81.83 ± 13.99 μg/dL. Meanwhile, the mean ± SD value of the serum zinc concentration in the control group was 86.66 ± 17.58 μg/dL. While the patients tend to have a lower zinc concentration in the serum compared with controls, the difference between the two groups was insignificant. Another similar study by Naseri *et al*.[14] observed the mean serum zinc concentration in the patient and control groups was 55.2 ± 9.6 and 55.8 ± 8.2 μg/100 mL, respectively. No significant difference in serum zinc concentration was found between the two groups (P = 0.795).

Another similar study by Raza *et al*.[12] observed serum zinc level was low in 42 (56%) patients and 24 (32%) controls (P = 0.003). Among the patients, serum zinc level ranged from 69.5 to 109 μg/dL with a mean of 83.6 + 91.04 μg/dL among controls (P = 0.044). Ranjit *et al*.[13] observed the difference in mean serum zinc levels in cases (80.50 ± 37.24 μg/dL) and controls (104.31 ± 25.31μg/dL) was statistically significant (P = 0.0001). A strong association between low serum zinc level and cutaneous viral warts was seen with odds ratio of 7.37 (95% CI = 1.98–27.31; P = 0.0028). Serum zinc level was negatively correlated with number of lesions (P = 0.001), largest size of the lesion (P = 0.039), and site of the lesions (P = 0.002).

In our study, zinc deficiency was not observed among the study group with cutaneous warts, on the contrary, we observed an increased level of serum zinc in cases with cutaneous warts. Furthermore, multicentric studies with larger sample sizes are needed to further investigate the role of serum zinc in multiple cutaneous warts.

Conclusion

From the study, we concluded the mean serum zinc levels in patients with multiple cutaneous warts were significantly higher than that of controls, which is contrary to many other studies. Our study also reported there was no significant association between serum zinc levels and duration or number of warts. Furthermore, a multicentric study with a larger sample size and therapeutic interventional trial could further establish the relation between serum zinc levels and cutaneous warts. This could bring potential prognostic and therapeutic applications in patients with multiple cutaneous warts, in the future.

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.

References

1. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsagué X, Shah KV, *et al*; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518-27.

2. Schiffman M, Castle PE. Human papillomavirus: Epidemiology and public health. Arch Pathol Lab Med 2003;127:930-4.
3. De Villiers E M, Fauquet C, Broker TR, Bernard H-U, Zur Hausen H. Classification of papillomaviruses. Virology 2004;324:17-27.
4. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al*. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12-9.
5. Chasapis CT, Loutsidou AC, Spiliopoulou CA, Stefanidou ME. Zinc and human health: An update. Arch Toxicol 2012;86:521-34.
6. Prasad A SZ. Role in immunity, oxidative stress and chronic inflammation. Curr Opin Clin Nutr Metab Care 2009;12:646-52.
7. Muzzioli M, Stecconi R, Moresi R, Provinciali M. Zinc improves the development of human CD34+ cell progenitors towards NK cells and increases the expression of GATA-3 transcription factor in young and old ages. Biogerontology 2009;10:593604.
8. Mocchegiani E, Muzzioli M, Giacconi R, Cipriano C, Gasparini N, Franceschi C, *et al*. Metallothioneins/PARP-1/IL-6 interplay on natural killer cell activity in elderly: Parallelism with nonagenarians and old infected humans. Mech Ageing Dev 2003;124: 459-68.
9. Mun JH, Kim SH, Jung DS, Ko H-C, Kim B-S, Kwon K-S, *et al*. Oral zinc sulfate treatment for viral warts: An open-label study. J Dermatol 2011;38:541-5.
10. Nofal A, Albalat W, Ismail A, Khattab FM. Immunotherapeutic modalities for the treatment of recalcitrant plantar warts: A comparative study. J Dermatolog Treat 2022;33:922-7.
11. Luong TN, Nguyen CT, Firas AN. Serum zinc level in patients with severe genital warts: A case-control study in a dermatology hospital. Infect Dis Obstet Gynecol 2022;8:2022.
12. Raza N, Khan DA. Zinc deficiency in patients with persistent viral warts. J Coll Phys Surg Pak 2010;20:83-6.
13. Ranjit A, Rajbhandari SL, Gautam N, Poudyal Y. Association between serum zinc level and cutaneous viral warts: A case control study. Nepal J Dermatol Venereol Leprol 2019;17:17-21.
14. Naseri M, Shahbaz S, Handjani F, Ghariheh A. Serum zinc levels in patients with multiple warts. J Pak Assoc Dermatol 2009;19:4-8.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 03/06/2024

Eumycetoma, A Report of Two Rare Cases

Swagata A. Tambe, Kirti M. Jangid, Manali S. Wanare, Ketki S. Bhoite

Department of Dermatology, Seth V.C. Gandhi & M.A Vora Municipal General Hospital, Mumbai, Maharashtra, India

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

Abstract

Mycetoma is a chronic, slowly progressive, suppurative, granulomatous disease of the subcutaneous tissue characterized by a localized swelling with multiple sinuses discharging granules that are micro-colonies of the causative agents. Eumycotic mycetoma is caused by saprophytic fungi. It is responsible for considerable physical comorbidity, as many cases may require surgical interventions, including amputations. Facilities for tissue culture and sensitivity testing may not be available at resource poor settings, adding to the disease burden. Identification of organisms and appropriate therapy is essential for a successful treatment outcome. Here, we present two rare cases of eumycetoma caused by Aspergillus.

Keywords: Aspergillus, eumycetoma, fungal

Introduction

Mycetoma has been acknowledged as a neglected tropical disease (NTD) by the World Health Organization (WHO) in 2016. It was first described in the Madurai district of Tamil Nadu, India. It is more common in males and usually presents between 20 and 50 years of age. It is classified into 2 types: Actinomycetoma and eumycetoma, depending on the causative agent. The highest incidence is reported from the "mycetoma-belt," which includes the equatorial regions of Africa, Latin America, and Asia. The majority of cases in India are actinomycotic. In India, eumycetoma is more commonly reported from North India, whereas actinomycetoma is commonly reported from Andhra Pradesh, West Bengal, Madhya Pradesh, and Tamil Nadu.[1] The most common species of fungi causing eumycetoma are Madurella and Leptosphaeria. Aspergillus is a ubiquitous fungi, opportunistic, filament-forming with over 180 different species. These are found in water, soil, air, plants, etc., and it is a rare etiological agent for mycetoma. Appropriate diagnosis and effective therapy are essential to avoid the high morbidity resulting from the disease.

Case Report

Case 1

A 60-year-old male resident of Jabalpur, working in the food industry, presented with a diffuse, ill-defined, indurated, tender, nodular, firm swelling studded with sinuses discharging purulent and serosanguineous discharge consisting of white grains affecting the dorsal and plantar aspects of the left foot for fifteen years. The overlying skin was hyperpigmented and indurated [Figure 1]. The regional lymph nodes did not show any significant enlargement and systemic examination was unremarkable. There was no history of preceding trauma. He was a known diabetic on oral hypoglycemic agents.

Histopathology of the grain revealed pale eosinophilic grains composed of multiple interlacing hyphae with club-shaped ends surrounded by an inflammatory infiltrate of neutrophils [Figure 2A]. Grocott–Gomori staining revealed numerous black-stained fungal hyphae

Submission: 24-Sep-2023 **Revision:** 10-Dec-2023
Acceptance: 20-Dec-2023 **Web Publication:** 01-Feb-2024.

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_100_23

Address for correspondence: Dr. Kirti Jangid, Department of Dermatology, OPD no. 18, 2nd Floor, OPD Building, Seth V.C. Gandhi & M.A Vora Municipal General Hospital, MG Road, Ghatkopar East, Mumbai 400077, Maharashtra, India.
E-mail: kirtijangid@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Tambe SA, Jangid KM, WanareMS, Bhoite KS. Eumycetoma, a report of two rare cases. Turk J Dermatol 2023;17:152-7.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024



Figure 1: (a) Case 1: Diffuse, ill-defined indurated tender firm swelling of the left foot. Discharging sinuses, and nodules are present on the medial aspect of the left foot. (b) Case 1: Discharging sinuses and a few healed sinuses on the left sole. (c) Case 1: Discharging sinuses and few healed sinuses on the dorsum of left foot with hyperpigmented and indurated skin

and larger thick chlamydospores [Figure 2B]. Periodic Acid Schiff (PAS) stain revealed pinkish-stained broad club-shaped hyphae [Figure 2C]. Fungal culture of grains revealed the growth of Aspergillus species sensitive to ketoconazole and fluconazole and resistant to itraconazole.

X-ray of the left foot (anteroposterior/lateral) showed soft tissue swelling without bony abnormality. Local ultrasonography revealed an ill-defined, hypodense collection in the subcutaneous plane with multiple sinuses. Laboratory investigations were normal.

The patient was treated with oral ketoconazole 200 mg twice daily and a saturated solution of potassium iodide, 5 drops 3 times a day, which was gradually increased to 40 drops 3 times a day with regular monitoring of liver function tests and thyroid function tests for 6 months. The patient started improving with a reduction of swelling and resolution of the sinuses [Figure 3]. He is currently under regular follow-up with continued medical treatment in the form of a tablet Ketoconazole and a saturated solution of potassium iodide.

Case 2

A 43-year-old married female, a housemaid from Mumbai, presented with a tender, ill-defined swelling of the right foot with firm induration and local warmth [Figure 4A] for 8 months, causing difficulty in walking. There was no history of any major medical or surgical illness.

USG of the local part showed multiple hypoechoic areas in the dermis and subcutaneous tissue [Figure 4B]. MRI revealed ill-defined marrow edema at the base of the fourth and fifth metatarsal bones without bony destruction. Skin biopsy revealed a chronic inflammatory infiltrate composed of lymphocytes, epithelioid cells, and histiocytes [Figure 4C]. Fungal culture of tissue samples revealed growth of Aspergillus species sensitive to itraconazole. Her routine hematological investigations, including blood sugars, were normal. The patient was treated with oral itraconazole 200 mg twice daily for 8 months, resulting in complete resolution of the lesion, which was confirmed on repeat ultrasonography [Figure 5]. The patient improved well with no signs of recurrence during a follow-up period of 3 years.

Discussion

The prevalence of eumycetoma in India is less than 0.01 cases per 100,000 inhabitants.[2] It most commonly affects field laborers. The most common site of infection is the lower extremity followed by the hand, head, neck, chest, shoulder, and arms. The most common causative organism is *Madurella mycetomatis*.

The disease is characterized by a triad of painless, firm, subcutaneous swelling, multiple sinuses, and discharging granules. Actinomycetoma is the closest differential diagnosis of eumycetoma. The differentiating features between the two diseases are mentioned in Table 1.[3] Skin biopsy with hematoxylin and eosin staining shows

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

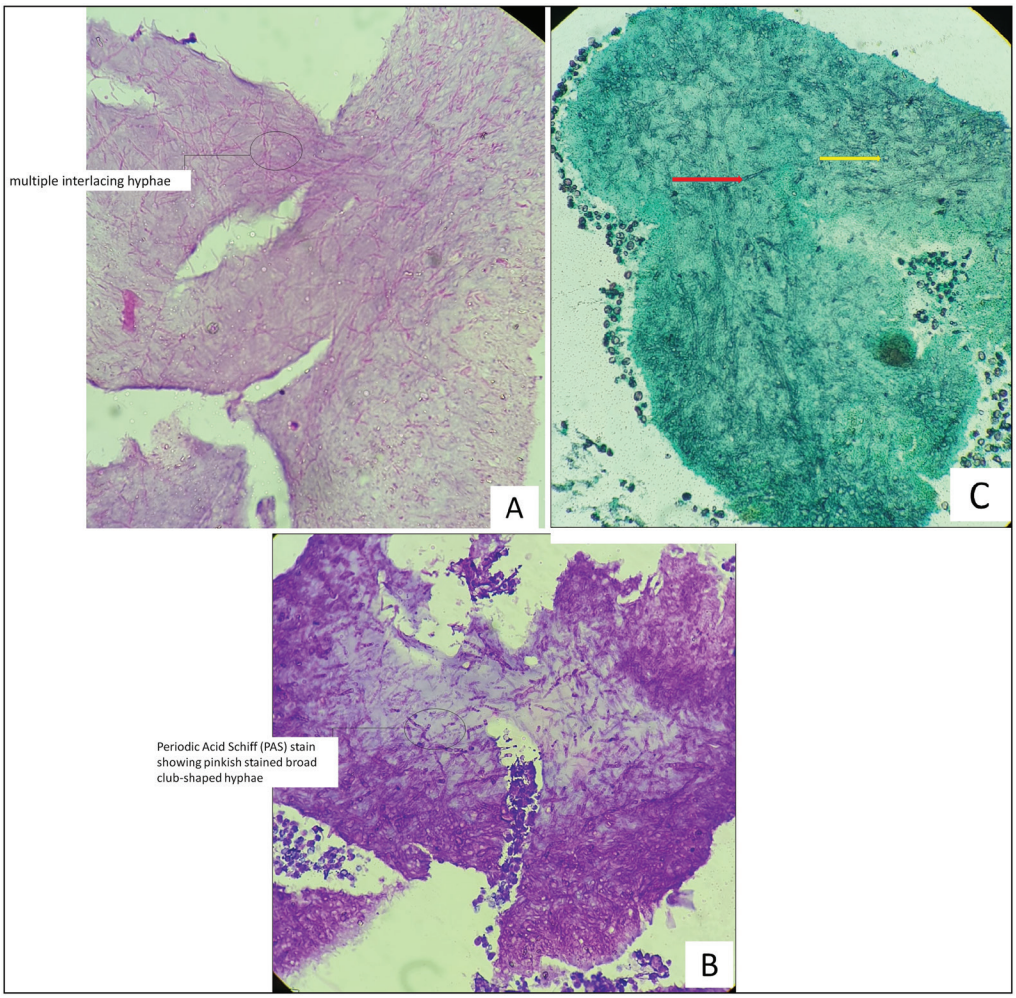


Figure 2: (a) Histopathology of grain showed pale eosinophilic grains surrounded by inflammatory infiltrate of neutrophils. Grains were composed of multiple interlacing hyphae with club-shaped ends. (b) Periodic Acid Schiff (PAS) stain revealed pinkish-stained broad club-shaped hyphae. (c) Grocott–Gomori staining revealed numerous black-stained fungal hyphae (red arrow) and large thick chlamydospores (yellow arrow)

suppurative granulomas surrounding characteristic grains that are present in the subcutaneous tissue. In eumycetoma, these grains are aggregates of septate and branched, radially arranged broad hyphae. Periodic acid–Schiff and Grocott–Gomori staining may be performed for the demonstration of fungal hyphae. Culture of grains or biopsy samples in special media such as Sabouraud 4% dextrose agar or Kimmig's agar at 37°C for 4–6 weeks provides identification of the causative agent.

Various imaging modalities may be utilized to assess the extent of the disease. X-ray studies may reveal periosteal erosion, osteoporosis, osteomyelitis, osteolysis, and osteosclerosis.

Further, ultrasonography may reveal single or multiple thick-walled cavities without acoustic enhancement, with grains having hyper-reflective echoes.

Magnetic resonance imaging (MRI) is the most detailed method for assessing bone and soft tissue involvement.[4,5]

Serological tests like enzyme-linked immunosorbent assay may be used for detecting circulating antibodies.[6]

The appropriate treatment of mycetoma depends on precise species identification and the extent of the disease. Triazole antifungals (such as itraconazole) are the treatment of choice for eumycetoma, and usually, a prolonged treatment of 1–2 years is required.[7,8] Potassium iodide (KI) gets concentrated in infected granulomas and necrotic tissues, inhibiting further granuloma formation. Its combination with itraconazole leads to an enhanced therapeutic effect in eumycetoma.[7-9]

The fungal isolate in both of our cases was identified as Aspergillus. Species identification could not be done due to a lack of resources. Aspergillus is a rare cause of eumycetoma in India. A summary of cases

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024



Figure 3: (a) Case 1: Healing of lesions on the medial aspect of the left foot. (b) Case 1: Healing of lesions on the medial aspect of the left sole. (c) Case 1: Healing of lesions on the dorsal aspect of the left sole

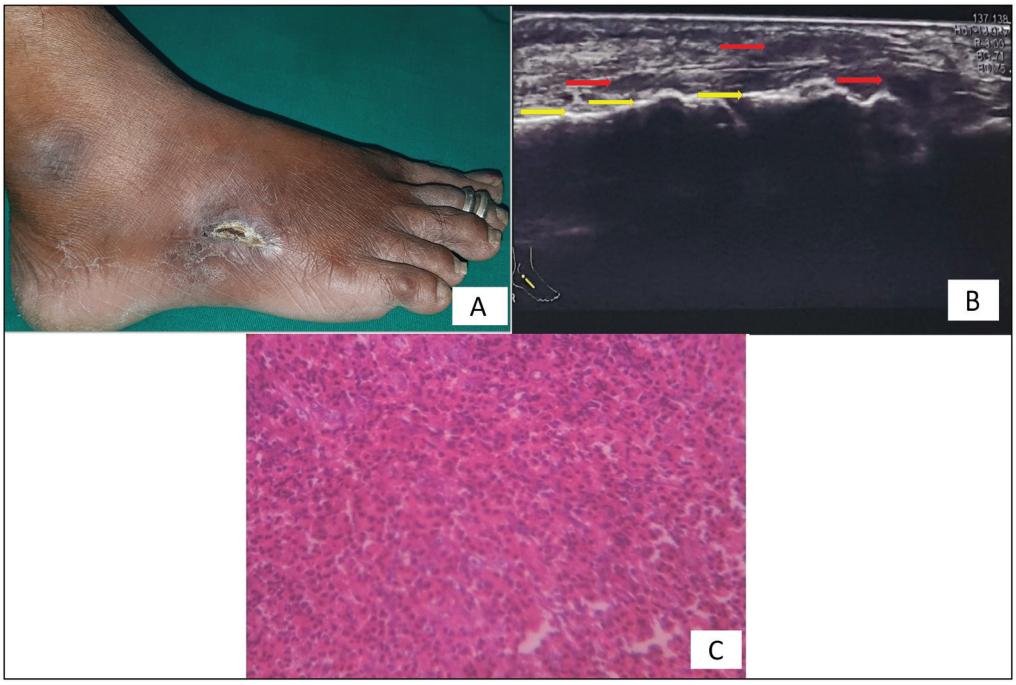


Figure 4: (a) Case 2: Tender ill-defined swelling studded with discharging sinuses, discoloration of the right foot with firm induration and local warmth. (b) Case 2: USG of the local part showed multiple hypoechoic areas (red arrows) in the dermis and subcutaneous tissue suggesting sinus formations with mild periosteal reaction (yellow arrows). (c) Case 2: Deep biopsy revealed a chronic inflammatory infiltrate composed of lymphocytes, epithelioid cells and histiocytes in the dermis

of eumycetoma caused by Aspergillus species is mentioned in Table 2. The reported cases have shown male preponderance, with the most common site of involvement being the lower extremity. Most cases belonged to the age group of 45 to 65 years. *Aspergillus nidulans* and *Aspergillus flavus* grew in culture in two

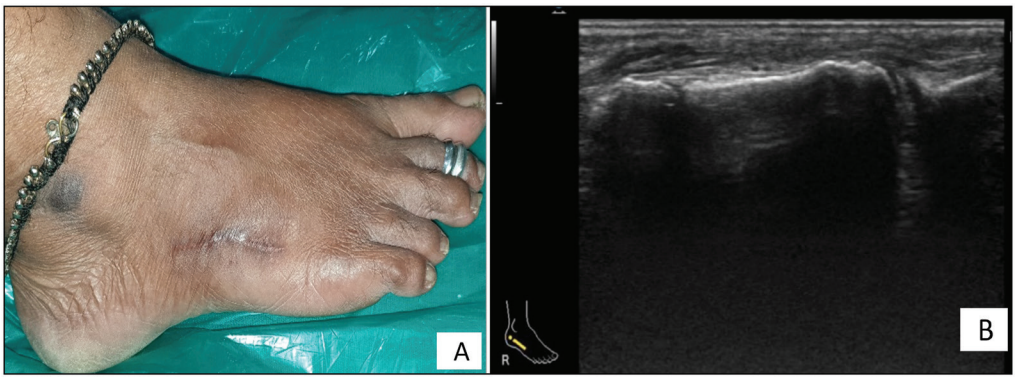


Figure 5: (a) Case 2: Clinical improvement after 8 months of treatment. (b) Case 2: Ultrasonography of the foot post-treatment showing resolution of sinuses

Table 1: The differentiating features of eumycetoma and actinomycetoma

Salient Features	Eumycetoma	Actinomycetoma
Epidemiology	More prevalent in humid areas, usually seen in Africa and India	More prevalent in drier areas, usually seen in Central and South America
Causative agent	Fungi	Bacteria
Common species	*Madurella mycetomatis* (70% of cases), Madurella grisea and Scedosporium apiospermum.	Nocardia brasiliensis, Actinomadura madurae, Actinomadura pelletieri, Streptomyces somaliensis
Characteristics of the causative organisms	Gram-negative, septate hyphae 4–5 microns thick	Gram-negative, fine, branching filaments, about 1 micron thick
Clinical characteristics	Less severe inflammation with fewer sinuses. Rarely disseminative, only invades the primary location, slower spread to bone structures	More severe inflammation with multiple sinuses, more rapid progression, rapid spread to underlying bone causing osteomyelitis
Granule color	Commonly black, white	White, yellowish-white, light red, red, cream, to brownish-yellow.
Bone anomaly	Slower spread to underlying bone structures	Rapid spread to bone structures
Management	•Ketoconazole •Itraconazole •Voriconazole •Posaconazole Surgery is usually definitive	•Trimethoprim-sulfamethoxazole •Amikacin-trimethoprim sulfamethaxozole •Amikacin •Rifampicin-gentamycin •Amikacin-imipenem •Linezolide

cases each. Two patients were diagnosed with type 2 Diabetes mellitus, and one patient was diagnosed with myelofibrosis and underwent allogeneic hematopoietic stem cell transplantation 1 year before presenting with skin lesions. Five of the total cases were reported from India, and the rest from Pakistan, Sudan, and the United States. Most of the cases were managed with oral itraconazole.

Our cases highlight the importance of histopathology, fungal culture, and sensitivity in the appropriate management of eumycetoma. Also, the use of ultrasonography as a noninvasive and less expensive modality to monitor the treatment response in patients of eumycetoma.

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.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024

Table 2: Summary of case reports of eumycetoma caused by Aspergillus species

Sr. no.	Age/sex	Site	Species identified	Comorbidities if any	Treatment	Authors	Geographical area of reporting
1	49-year-old male	Right foot	*Aspergillus niger*	None	Voriconazole 400 mg/day	Mallick *et al.*[10]	Karachi, Pakistan
2	45-year-old male	Right lower limb	*Aspergillus nidulans*	Type 2 diabetes mellitus	Itraconazole and potassium iodide	Prasanna *et al*[11]	Maharashtra, India
3	9-month-old-male baby	Left lower limb	*Aspergillus flavus*	None	Surgical curettage and debridement along with itraconazole (5 mg/kg/day)	Baishya *et al.*[12]	Assam, India
4	55-year-old male	Left foot	*Aspergillus flavus*	None	Voriconazole	Ahmed *et al*[13]	Sudan
5	61-year-old female	Dorsum of foot	*Aspergillus candidus*	None	Excision and itraconazole.	Kaur *et al.*[14]	Himachal Pradesh (India)
6	62-year-old male	Left foot and ankle	*Aspergillus sydowii*	None	Itraconazole 200 mg twice daily and terbinafine 250 mg daily	Vera-Cabrera *et al.*[15]	Not available
7	45-year-old male	Right lower limb and right thigh.	*Aspergillus nidulans*	Type 2 diabetes mellitus and hypertension	Oral itraconazole 200 mg twice daily	Verma *et al.*[16]	India
8	66-year-old male	Right thigh extending up to the knee	Aspergillus and penicillium	Myelofibrosis managed with allogeneic hematopoietic stem cell transplantation (HSCT) 1 year before presenting with skin lesions	Voriconazole and liposomal amphotericin b	Hopps *et al*[17]	United States
9	9-year-old boy	Right foot	Aspergillus species	None	Itraconazole 100 mg twice daily	Sawatkar *et al.*[18]	Rajasthan (India)

References

1. Van de Sande WW. Global burden of human mycetoma: A systematic review and meta-analysis. PLoS NeglTrop Dis 2013;7:e2550.
2. Chitrambalam TG, Sekhar S, Panicker KM, Sundaraj J. A case report of eumycetoma in the thigh: An unusual presentation as a lump. Int Surg J 2019;6:2988-90.
3. Reis CMS, Reis-Filho EGM. Mycetomas: An epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol 2018;93:8-18.
4. Sarris I, Berendt AR, Athanasous N, Ostlere SJ; OSIRIS Collaborative Study Group. OSIRIS collaborative study group MRI of mycetoma of the foot: Two cases demonstrating the dot-in-circle sign. Skeletal Radiol 2003;32:179-83.
5. Czechowski J, Nork M, Haas D, Lestringant G, Ekelund L. MR and other imaging methods in the investigation of mycetomas. Acta Radiol 2001;42:24-6.
6. Salinas-Carmona MC, Welsh O, Casillas SM. Enzyme-linked immunosorbent assay for serological diagnosis of Nocardia brasiliensis and clinical correlation with mycetoma infections. J Clin Microbiol 1993;31:2901-6.
7. Mahgoub ES, Gumaa SA. Ketoconazole in the treatment of eumycetoma due to Madurella mycetomii. Trans R Soc Trop Med Hyg 1984;78:376-9.
8. Agarwal P, Agarwal US, Gupta R. Eumycetoma foot—Successful treatment with combination of itraconazole and potassium iodide. JDA Indian J Clin Dermatol 2018;2:53-5.
9. Welsh O, Salinas MC, Rodríguez MA. Treatment of eumycetoma and actinomycetoma. Curr Top Med Mycol 1995;6:47-71.
10. Mallick YA, Yaqoob N, Aftab K, Mallick FA, Zahid QUA. Successful treatment of human eumycetomas caused by Aspergillus species with voriconazole. J Pak Assoc Dermatol 2021;31:15-22.
11. Prasanna S, Grover N, Bhatt P, Sahni AK. A case of *Aspergillus nidulans* causing white granule mycetoma. Med J Armed Forces India 2016;72:88-90.
12. Baishya L, Kalita M, Sharma A, Dutta B, Hazarika D. White grain eumycetoma due to Aspergillus flavus in infancy: A rare case report from Assam. J Pure Appl Microbiol 2017;11:969-73.
13. Ahmed SA, Abbas MA, Jouvion G, Al-Hatmi AMS, de Hoog GS, Kolecka A, *et al*. Seventeen years of subcutaneous infection by *Aspergillus flavus*; eumycetoma confirmed by immunohistochemistry. Mycoses 2015;58:728-34.
14. Kaur M, Singla N, Bhalla M, Kundu R, Gulati N, Chander J. Aspergillus candidus eumycetoma with review of literature. J Mycol Med 2021;31:101135.
15. Vera-Cabrera L, Cardenas-de la Garza JA, Cuellar-Barboza A, Gallardo-Rocha A, Molina-Torres CA, Escalante-Fuentes W, *et al*. Case report: Coral reef pathogen *Aspergillus sydowii* causing black grain mycetoma. Am J Trop Med Hyg 2021;104:871-3.
16. Verma R, Vasudevan B, Sahni AK, Vijendran P, Neema S, Kharayat V. First reported case of *Aspergillus nidulans* eumycetoma in a sporotrichoid distribution. Int J Dermatol 2015;54:74-7.
17. Hopps S, Roach A, Yuen C, Borders E. Treatment for a eumycetoma infection caused by Aspergillus in an immunocompromised host: A case report. Transpl Infect Dis 2015;17:94-7.
18. Sawatkar GU, Narang T, Shiva Prakash MR, Daroach M, Sharma M, Nahar Saikia U, *et al*. Aspergillus: An uncommon pathogen of eumycetoma. Dermatol Ther 2017;30. Doi: 10.1111/dth.12411.

Downloaded from http://journals.lww.com/tjod by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/06/2024