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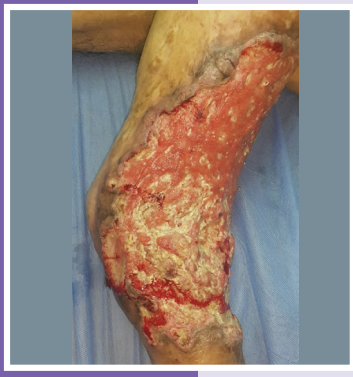

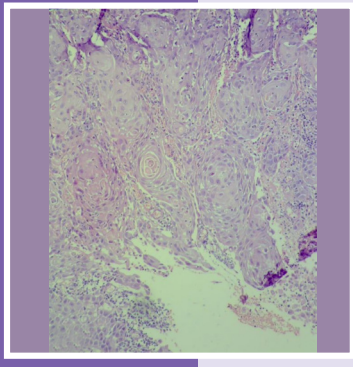

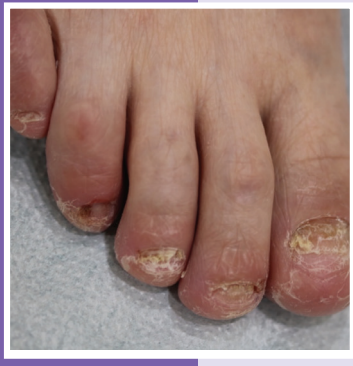



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the appendices

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Mareledwane NG. A randomized, open-label, comparative study of oral doxycycline 100 mg vs. 5% topical benzoyl peroxide in the treatment of mild to moderate acne vulgaris. Int J Dermatol 2006; 45: 1438-1439. PMID: 17184250

Doger FK, Dikicioglu E, Ergin F, Unal E, Sendur N, Uslu M. Nature of cell kinetics in psoriatic epidermis. J Cutan Pathol 2007; 34: 257-263. PMID: 17302610

**Book:** - Monsel G, Delaunay P, Chosidow O. Arthropods. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology, 9th ed. Singapore: Blackwell Science; 2016. p. 32-34.

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REVIEW

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# Drug Eruptions

Defne Özkoca, Tuğba Kevser Üstünbaş Uzunçakmak, Özge Aşkın, Server Serdaroğlu

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## ABSTRACT

Drug reaction are seen in the 8% of the general population; this number rises to 15% in the hospitalized patients. Drug eruptions can be classified according to the prognosis: benign reactions and malignant reactions. Second, they can be classified according to the clinical type as mild, moderate and severe reactions. This article dwells upon the clinical characteristics and treatment of drug eruptions.

Keywords: Drug, Moderate, Reaction, Severe

## Introduction

Drug reactions are defined by the American Association of Dermatologists as any unwanted change in the skin, skin appendages or mucous membranes due to a drug; and as any unpredicted and harming reaction observed due to a drugs given at doses within the normal limits by the World Health Organisation. The prequistes for a reaction to be considered as a drug reaction are [1,2]:

- The dosage of the drug was within the normal limits,
- The reaction was unpredictable,
- The reaction was harmful for the patient.

## Epidemiology

Drug reaction are seen in the 8% of the general population; this number rises to 15% in the hospitalized patients. The drugs that are known to cause unprectable reactions are penicillin, sulphonamides, non-steroidal anti-inflammatory drugs and anti-epileptic drugs. Symptoms are seen 8 to 21 days within the drug intake. The duration between the ingestion of the drugs and the initiation of the symptoms varies according to the disease presentation. The most commonly seen types of drug reactions are morbiliform drug reactions and urticaria; which are mild reactions that are not complicated [3,4,5].

Female patients are at increased risk for drug reactions compared to male patients. These reactions are seen more commonly in adults than in children. Patients of African American descent are at increased risk as well. Patients suffering of viral infections, eg. HIV, cytomegalovirus and Epstein-Barr virus, have a predilection for drug reactions. Comorbid diseases such as renal or hepatic insufficiencies increase the risk of drug reactions as well [6].

## Classification

There are two different classification schemes of drug reactions. First, it can be classified according to the prognosis: benign reactions and malignant reactions. Malignant reactions have the potential of being fatal and are seen in 0.1% of the population. Second, it can be classified according to the clinical type as mild, moderate and severe reactions [7].

## Severe Drug Reactions

Severe drug reactions require immediate diagnosis and treatment; and are as follows [3]:

- Anaphylaxis,
- Anticoagulant induced skin necrosis,
- Acute Generalised Exanthematous Pustulosis (AGEP),

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- Drug Induced Hypersensitivity syndrome [drug rash with eosinophilia and systemic symptoms (DRESS)],
- Generalised bullous fixed drug eruption,
- Steven-Johnson syndrome (SJS),
- Toxic epidermal necrolysis (TEN).

Symptoms suggestive of severe drug reactions are [3]:

- Fever,
- Facial edema,
- Lymphadenopathy,
- Bullous lesions,
- Pustuler lesions,
- Nikolsky positivity,
- Mucosal involvement,
- Systemic signs and symptoms,
- Peripheral eosinophilia, atypical lymphocytosis, increase in liver function test, increased creatinine in the laboratory work-out.

## Duration

The time interval between the initiation of drug intake and the appearance of lesions differs according to the type of reaction. The earliest are urticaria or angioedema, which ocur within minutes to hours. AGEP occurs in less than four days. Exanthematous drug reactions ocur within 4 to 14 days. SJS or TEN ocur in 7 to 21 days. The latest reaction is DRESS, which ocurs in 15 to 40 days [5].

## Mild (Non-complicated) Reactions

### 1. Urticaria and/or Angioedema

These reactions ocur within minutes to hours. The most common culprit drugs for urticaria are antibiotics such as penicilin, cephalosporins, sulphonamides and minocycline. Monoclonal antibodies, non-steroidal anitiinflammatory drugs and radiocontrast media may also cause urticaria or angioedema. Furthermore, aspirin or non-steroidal anti-inflamatory drugs may cause acute urticarial attacks in patients with chronic urticaria. Angioedema is frequently caused by penicilin, radiocontrast media, angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and monoclonal antibodies. H1 receptor antagonist antihistamines are used in the treatment of urticaria or angioedema along with the cessation of the culprit drugs [3].

### 2. Exanthematous Drug Eruption

Exanthematous drug reactions are also known as morbiliform drug reactions or maculopapuler drug reactions. This is the most frequently seen presentation of drug eruptions. It is seen within 7-14 days of the drug intake; this time interval decreases in the following exposures. The high risk drugs are aminopenicillin, cephalosporines, sulphonamides, allopurinol and aromatic anticonvulsants. The eruption starts at the trunks and upper extremities; is maculopapular and urticarial in character. It has symmetrical distribution. Mucosal involvement is not seen. Pruritus may be occasionaly seen. The differential diagnoses are viral exanthems in children. The symptoms cease without complication in a couple of weeks after the culprit drug is stopped. Supportive treatment is usually necessary: topical steroid formulations and oral antihistamines. Systemic streoid treatment may be necessary in recalcitrant cases [3].

### 3. Fixed Drug Eruption

Fixed drug eruption is seen a couple of days after the intake of the culprit drug. The recurrent attacks ocur within 24 hours. Clinically, one or more oval/circular erythematous and edematous macule with distinct borders are seen. Vesicles, bullae or erosions may be present as well. Lips, face, hands, feet and the genital region are the most frequent locations. The lesions ocur at the same locations in each attack; new locations may be added in recurrent attacks. The lesions fade away within several days, leaving post-inflammatory hyperpigmentation. The most frequent culprits are antibiotics (sulphonamides, tetracyclins, betalactams, flouroquinolones, macrolides), non-steroidal anti-inflammatory drugs, asetaminophen, aspirin, barbiturates, dapsone, proton-pump inhibitors and azole antifungals. Generalised bullous fixed drug eruption should be considered in patients with multiple lesions; and the prognosis is determined according to the extent of epidermal detachment. The treatment is composed of the cessation of the culprit drugs and topical steroid preperations [3].

## Potentially Fatal (Complicated) Reactions

### 1. AGEP

AGEP is also known as pustular drug reaction or toxic pustuloderma. It occurs within four days after the ingestion of the culprit drug. It is important to note that, AGEP presents earlier than exanthematous drug eruption. Multiple edematous small (<5 mm) non-follicular sterile pustules are observed on an erythematous base. Burning and pruritus are common; fever frequently accompanies the eruption. The lesions begin at the face and intertriginous areas; and distrubute witihin hours. Facial and acral edema may also be observed. Neutrophilic leukocytosis, mild eosinophilia, increased liver and renal function test and hypocalcemia are observed on the lab work-out. Subcorneal spongioform pustules are seen in the histopathology. The most frequent causes are antibiotics (aminopenicillins, sephalosporins, clindamycin, sulphonamides, metranidazole), calcium canal blockers (especially diltiazem), hydroxychloroquine, non-steroidal anti-inflammatory drugs,

acetaminophene, terbinafin and proton pump inhibitors. Pustuler psoriasis and TEN may be considered in the differential diagnoses according to the clinical presentation. Treatment includes the cessation of the culprit drugs, oral antipyretics, topical steroids and systemic cyclosporine or corticosteroids if necessary [3].

### 2. DRESS

DRESS occurs 2 to 6 weeks after the ingestion of the culprit drug, later compared to other drug reactions. Fever accompanies the typical rash that starts morbilifom and then becomes edematous that is showing follicular accentuation. The rash starts at the face, abdomen and upper extremities. Mucosal involvement is not frequent, and is mild if it is present. Liver and renal functions are affected. Lymphadenopaties are seen Facial edema and eosinophilia are characteristic. The most frequent culprit drugs are aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital) and sulphonamides. Less frequently minocycline, allopurinol, dapsone and abacavir may cause DRESS. Maculopapuler drug eruption can be considered in the differential diagnosis due to the cutaneous lesions; however, organ involvement differentiates these two diseases. The culprit drug should be stopped and topical steroids are added in mild cases. Systemic steroids can be added in severe cases [3].

### 3. SJS and TEN

Both SJS and TEN have high mortality and morbidity. The risk is especially increased in the elderly and HIV positive patients. The symptoms suggestive of SJS and TEN are mucosal involvement, flaccid vesicles and bullae, nikolsky positivity, fever and pain. Symptoms ocur 7-21 days after the ingestion of the drug. Erythematous, dusky macules and patches appear at first, flaccid bullae ocur within hours to days. The disease spectrum is determined according to the body surface area that shows epidermal detachment. If less than 10% is detached SJS is considered. If greater than 30% is detached TEN is considered. Oral mucosa is affected in 70% of the patients, ocular symptoms are seen in 75% of the patients. Gastrointestinal, genitourinary or pulmonary symptoms may be seen as well. The differential diagnoses include erythema multiforme major, generlized fixed drug eruption, staphylococcic scalded skin syndrome, autoimmune bullous diseases and exfoliative erythroderma. Biopsy can be used to differentiate [5].

Mortality is up to 30% in TEN. On the contrary, SJS has a 5% mortality rate. The treatment includes the cessation of the culprit drug and hospitalisation at the intensive care unit. Supportive treatments such as antibiotics and hydration are often necessary. Topical treatment with antibiotics, wet dressings and epitelizing agents are beneficial. Systemic steroids, intravenous immunoglobulins and cyclosporine are contraversial therapies [5].

### Ethics

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### Authorship Contributions

Concept: D.Ö., T.K.Ü.U., Ö.A., S.S., Design: D.Ö., T.K.Ü.U., Ö.A., S.S., Literature Search: D.Ö., T.K.Ü.U., Ö.A., S.S., Writing: D.Ö., T.K.Ü.U.

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ORIGINAL ARTICLE

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# Increased Adverse Skin Reactions Among Healthcare Workers During COVID-19 Outbreak

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## ABSTRACT

**Background:** The personal protective equipment (PPE) and frequent hand hygiene procedures needed during the Coronavirus disease-2019 outbreak impair skin integrity in healthcare workers (HCWs). We aimed to evaluate the prevalence and risk factors of adverse skin reactions related to infection-prevention measures among HCWs

**Materials and Methods:** A questionnaire survey was administered to evaluate the duration of PPE, disinfectant, and moisturizing agent use, as well as handwashing frequency among our hospital's HCWs.

**Results:** The questionnaire was completed by 702 HCWs with a mean age of 34.8±9.8 years-old. Adverse skin reactions were reported by 79.5% of our participants. Hands (63.5%) and face (48.9%) were the most commonly affected areas. Female sex, being a doctor/nurse, having a history of underlying chronic dermatoses, and PPE usage more than six hours per day were increased the risk of adverse skin reactions. Handwashing more than 10 times/day and moisturizing less than 5 times/day were also related to increased adverse skin reactions. In HCWs, wearing more than one mask was associated with pressure-induced skin changes on the face and triggering herpes labialis.

**Conclusion:** Hand hygiene-associated dermatitis is triggered by frequent handwashing and less moisturizing among HCWs. Surgical masks may also be just as responsible as N95 masks for causing facial skin damage.

**Keywords:** COVID-19, Hand disinfection, Personal protective equipment, Healthcare workers

## Introduction

Since the Coronavirus disease-19 (COVID-19) pandemic worldwide, healthcare workers (HCWs) have had to use personal protective equipment (PPE) for long hours and to pay more attention to hand hygiene by frequent hand washing and use of alcohol-based disinfectants. This has made HCWs susceptible to skin damage as a result of infection-prevention measures [1]. In this study, a questionnaire survey was conducted that included questions about the occurrence of skin reactions and the frequency or duration of conducting infection-prevention measures. The goal was to evaluate the prevalence, clinical characteristics, and risk factors of skin reactions among Turkish HCWs during the COVID-19 outbreak. Our results were also compared with similar studies reported worldwide in the literature [2,3,4,5,6]. The findings of our study, accompanied by data from the literature review, will help to determine whether infection-prevention measures pose important occupational health risks in HCWs during the COVID-19 pandemic.

## Materials and Methods

This survey was conducted in a tertiary healthcare center by the distribution of a cross-sectional questionnaire that asked about the duration of the use of PPE and gloves, the frequency of handwashing, the use of alcohol-based disinfectants, and hand

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cream application. Participants in this study were medical doctors, nurses, and other healthcare professionals. Demographics, adverse skin reactions, and sites of lesions were recorded. Univariate and multivariate analyses were used to evaluate associations between adverse skin reactions and the following parameters: age, sex, occupation, duration of exposure to PPE, layers and types of gloves, frequency of handwashing, and hand cream application.

### Statistical Analysis

The Statistical Package for the Social Sciences version 22 was used for analysis of the data. The independent t-test, chi-square and Fisher Exact tests were performed to compare the groups. Quantitative data are expressed in the tables as mean ± standard deviation values. Categorical data are presented as numerical values (n) and percentages (%). Multivariate analysis was performed using logistic regression analysis from the parameters that were significant in univariate analysis. Data were analyzed at a 95% confidence level, and a p value of <0.05 was considered statistically significant. All participants signed an informed consent form before the questionnaire survey. The study was approved by the Ethics Committee of Haseki Istanbul Training and Research Hospital and was carried out in accordance with the Declaration of Helsinki.

## Results

The questionnaire was completed by 702 HCWs with a mean age of 34.8±9.8 years; 400 (57%) were women. Among the respondents, 30.8% were medical doctors, 35.2% were nurses, and the rest were other HCWs (34%). A total of 558 (79.5%) respondents had adverse skin reactions (Table 1). The hands (63.5%) and face (48.9%) were the most commonly affected areas.

The univariate analysis revealed that sex, occupation, underlying chronic dermatoses, and duration of exposure to PPE were significantly associated with an adverse skin reaction (Table 1). The multivariate analysis, female sex demonstrated that being a medical doctor/nurse, having a history of underlying chronic dermatoses, and experiencing a duration of exposure to PPE of more than six hours per day were associated with an increased risk of adverse skin reactions (Table 1).

Most of the HCWs washed their hands and/or used disinfectants more than 10 times per day (78.1% and 66.2%, respectively); however, only 28.2% applied hand cream more than 5 times per day. The univariate analysis indicated a significant association between adverse skin reactions on the hands and the frequency of hand washing, the number of moisturizing applications per day and the number of gloves worn (Table 2). The multivariate analysis revealed that adverse skin reactions on the hands were also associated with hand washing more than 10 times per day and with hand moisturizing less than 5 times per day (Table 2).

Adverse skin reactions noted on the face were pressure-induced skin changes (54.3%), the triggering (28.8%) and exacerbation (27.8%) of acne vulgaris and/or acne rosacea, and the triggering of herpes labialis (22.8%) (Table 3). Wearing more than one mask layer was associated with pressure-induced skin changes and exacerbation

**Table 1. Analysis of the risk factors for development of adverse skin reactions**

| Variable | Adverse skin reaction | | Univariate analysis | Multivariate analysis | |
|---|---|---|---|---|---|
| | Yes (n=558) (%) | No (n=144) (%) | p value | OR (95% CI) | p value |
| **Age (years, mean±SD)** | 34.5±9.7 | 36.0±9.9 | 0.060 | | |
| **Sex** | | | | | |
| - Male (n=295) | 67.1 | 32.9 | **0.001** | **3.28 (2.18-4.93)** | **0.001** |
| - Female (n= 400) | 88.75 | 11.25 | | | |
| **Working area** | | | | | |
| - COVID-19 related (n=420) | 80.9 | 19.1 | 0.429 | | |
| - Other (n=282) | 77.3 | 22.7 | | | |
| **Occupation** | | | | | |
| - Medical doctor/nurse (n=469) | 84 | 16 | **0.001** | **1.81 (1.20-2.72)** | **0.004** |
| - Other medical staff (n=230) | 70.4 | 29.6 | | | |
| **Underlying chronic dermatoses** | | | | | |
| - Yes (n=231) | 89.2 | 10.8 | **0.001** | **2.38 (1.47-3.86)** | **0.001** |
| - No (n=471) | 63.1 | 36.9 | | | |
| **Duration of PPE per day** | | | | | |
| <6 hours (n=321) | 74.1 | 25.9 | 0.001 | 1.93 (1.29-2.88) | **0.001** |
| ≥6 hours (n=380) | 84 | 16 | | | |

PPE: Personal protective equipment, CI: Confidence interval, SD: Standard deviation, COVID-19: Coronavirus disease-2019, OR: Odds ratio

of acne vulgaris and/or acne rosacea, whereas triggering of acne vulgaris and/or acne rosacea was more commonly reported by HCWs who wore a single mask layer (Table 3). In addition, triggering of herpes labialis was more common in our study in HCWs who wore only a single surgical mask layer. No significant relationship was found between the eye protection method and adverse skin reactions on the face in our study (Table 3).

## Discussion

Skin damage due to by infection-prevention measures among HCWs has recently been reported in various countries all over the world [2,3,4,5,6]. Our study provides awareness about the risk factors and prevalence for adverse skin reactions associated with infection-prevention measures during the COVID-19 pandemic in Turkey and can be generalized worldwide based on our literature review.

Adverse skin reactions were reported by 79.5% of our respondents, consistent with results of other studies [2,7]. Sex is known to be a risk factor for some dermatological diseases, and women were found to have an especially higher risk for dermatological complaints during the pandemic in our study, in agreement with some of the previous studies [2,4,5,6]. A lower threshold for reporting adverse skin reactions might be related with the higher prevalence of skin symptoms among women.

Skin barrier dysfunction and potential disorder of the skin microbiota of HCWs with underlying chronic dermatoses might be related to observing more common adverse skin reactions in these subjects [5]. The risk of adverse skin reactions in our study was higher for HCWs wearing PPE for more than six hours than for those exposed for less time, in line with previous reports [5,7,8]. Interestingly, the working area of the HCWs was not related to the development of adverse skin reactions in our study. A previous study that compared occupational hand eczema between workers in a surgical unit and healthcare professionals in the COVID-19 intensive care unit revealed a significant increase in the development of acute hand dermatitis among all participants, regardless of direct contact with COVID-19 patients, in agreement with our findings [9].

In our study, the hands (63.5%) were the most commonly affected body part in our HCWs during the pandemic. Similar to previous reports, more frequent (>10 times per day) hand washing, coupled with less frequent hand moisturizing (less than 5 times per day) increased the risk of hand skin damage in our study [4,5,7]. A previous evaluation of dermatological complaints among HCWs found that xerosis and eczema on the hands was increased by 2.44 and 3.57 times, respectively, while hand washing 10 times a day with a hand washing time longer than 10 seconds increased the risk of eczema 5.44 times [4]. The frequency of disinfectant application was not a statistically significant risk factor for hand skin damage in

**Table 2. Analysis of risk factors for development of adverse skin reaction on hands**

| Variable, (n=) | Adverse skin reaction (hand) | | Univariate analysis | Multivariate analysis | |
|---|---|---|---|---|---|
| | Yes (n=446) (%) | No (n=256) (%) | p value | OR (95% CI) | p value |
| **Frequency of hand washing per day** | | | | | |
| <10 (n=154) | 47.4 | 52.6 | **0.001** | 2.29 (1.56-3.35) | **0.001** |
| ≥10 (n=548) | 68.1 | 31.9 | | | |
| **Frequency of disinfectant use per day** | | | | | |
| <10 (n=237) | 60.3 | 39.7 | **0.209** | | |
| ≥10 (n=465) | 65.2 | 34.8 | | | |
| **Frequency of hand moisturing per day** | | | | | |
| <5 (n=504) | 65.7 | 34.3 | **0.001** | 1.57 (1.11-2.23) | **0.011** |
| ≥5 (n=198) | 58.1 | 41.9 | | | |
| **Features of gloves** | | | | | |
| - Powdered (n=169) | 58 | 42 | **0.196** | | |
| - Non-powdered (n=522) | 65.5 | 34.5 | | | |
| **Features of gloves** | | | | | |
| - Latex (n=605) | 63.5 | 36.5 | **0.925** | | |
| - Nitril (n=90) | 64.4 | 35.6 | | | |
| **Layers of gloves** | | | | | |
| One (n=489) | 59.9 | 40.1 | **0.006** | 0.47 (0.08-2.49) | **0.088** |
| More than one (n=207) | 72.5 | 27.5 | | | |

CI: Confidence interval, OR: Odds ratio

our study. Interestingly, previous studies suggested the application of alcohol-based disinfectants instead of soaps for hand hygiene, due to the high antimicrobial effect and low risk of skin reactions, supporting our finding regarding disinfectants [1,10,11].

The long-term use of gloves has also been reported to increase the risk of xerosis and dermatitis on the hands [12]. However, another study also indicated a considerably increased risk even with short-term glove use for 1 to 2 hours [4]. The virus that causes COVID-19 can exist for several hours on used PPE, so double gloving is recommended to reduce the risks of viral contamination during PPE removal [2,13]. However, wearing more than one layer of gloves increased the risk of hand skin damage in our study. Hypoallergenic gloves, such as nitrile and vinyl gloves, have been recommended for the prevention of hand dermatitis among HCWs, [11] but our findings did not show any statistically significant difference between latex and nitrile gloves.

Previously, various adverse skin reactions were reported in more than a third of HCWs who wore N95 masks [12]. In our study, 28.8% and 27.8% of our patients reported triggering and exacerbation of acne vulgaris and acne rosacea, respectively, due to masks, and the presence of pressure-induced skin changes on the face was noted in 54.3% of the HCWs. The N95 masks have been reported to cause more adverse skin reactions on the face than surgical masks due to higher air impermeability and more local pressure [14]. However, the findings of our study did not support this difference, as the occurrence of adverse skin reactions did not differ between N95 and surgical masks in our study. The exception was the triggering of herpes labialis, which was more common in HCWs who wore surgical masks.

Some studies evaluating skin reactions due to N95 and surgical mask wear among HCWs have indicated that N95 masks are associated with more reactions than other medical masks, in contrast with the results of our study [5,14]. Interestingly, another study evaluated several skin parameters, including skin hydration, transepidermal water loss, erythema, pH, and sebum secretion, on areas covered by the N95 and medical masks versus uncovered skin. At 2 and 4 hours of wear, and at 0.5 and 1 hour after taking off the masks, no significant differences were found between the N95 and medical masks for any of the skin parameters [14]. These previous findings may explain why no significant differences were noted between N95 and surgical masks regarding pressure-induced skin changes or triggering and exacerbation of acne vulgaris and/or acne rosacea in our study. A previous self-questionnaire study evaluating face mask-induced itch among members of the general public also showed no significant difference between in wearers using a surgical mask, cloth mask, or N95 mask, in agreement with our study [15]. In some previous studies, HCWs who wore surgical masks, paper masks, and cloth masks did not report any adverse skin reactions [6,12].

A fivefold increase in acne complaints was previously reported for the use of any mask type [4]. The flare-up of acne caused by long-time mask-wearing during the COVID-19 pandemic has been reported among the general population and was associated primarily with medical masks [16]. Friction or bursting of comedones, occlusion of pilosebaceous ducts, and formation of a wet environment conducive to bacterial proliferation may be responsible for the acne complaints related to mask use [11]. Another study evaluating the PPE induced facial dermatoses in HCWs found that goggles were the most common equipment among all PPE to cause any of the dermatoses, with N95 masks and face shields being the next major causes [17]. Conversely, in our study, no significant relationship was noted between eye protection methods and adverse skin reactions on the face.

### Study Limitations

Our study has some limitations. In our study, there may be an answer bias depending on the answers given by the healthcare professionals themselves. This is a self-administered questionnaire

**Table 3. Analysis of risk factors for development of adverse skin reaction on face**

| Variables | Pressure-induced skin changes (n=381) | Triggering of acne vulgaris and/or acne rosacea (n=202) | Exacerbation of acne vulgaris and/or acne rosacea (n=195) | Triggering of herpes labialis (n=160) |
|---|---|---|---|---|
| **Layers of mask**<br>- One (n=489) | **p=0.046**<br>200/489 (40.9%) | **p=0.012**<br>98/489 (20%) | **p=0.025**<br>96/489 (19.6%) | **p=0.122**<br>98/489 (20%) |
| - More than one (n=207) | 181/207 (87.4%) | 10/207 (4.8%) | 99/207 (47.8%) | 62/207 (30%) |
| **Features of mask**<br>- N95 (n=109)<br>- Surgical (n=346) | **p=0.458**<br>58 (53.2%)<br>170 (49.1%) | **p=0.260**<br>31 (28.4%)<br>80 (23.1%) | **p=0.427**<br>30 (27.5%)<br>83 (24%) | **p=0.024**<br>15 (13.8%)<br>83 (24%) |
| **Eye protection**<br>- None (n=191) | **p=0.133**<br>96 (50.3%) | **p=0.181**<br>55 (28.8%) | **p=0.387**<br>48 (25.1%) | **p=0.106**<br>48 (25.1%) |
| - Goggles (n=151) | 83 (55%) | 35 (23.2%) | 37 (24.5%) | 32 (21.2%) |
| - Face shields (n=207) | 107 (51.7%) | 59 (28.5%) | 65 (31.4%) | 37 (17.9%) |
| - Both (n=153) | 95 (62.1%) | 53 (34.6%) | 45 (29.4%) | 43 (28.1%) |

study analyzing the adverse skin reactions as felt by respondents, rather than as evaluated by dermatologists.

## Conclusion

Our study demonstrates that HCWs, and especially females with a history of underlying chronic dermatosis and with a longer exposure time to PPE wear, are particularly affected by adverse skin reactions in Turkey. Hand skin damage is triggered primarily by frequent hand washing, but less frequently by hand moisturizing. The findings in our study also suggest that surgical masks may be just as responsible as N95 masks for causing facial skin damage. This information may be useful for interventions intended to minimize the dermatological complaints of HCWs triggered by infection-prevention measures that impact their performance and quality of life.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Istanbul Haseki Training and Research Hospital (number: 127, date: 24/06/2020).

**Informed Consent:** This study was performed followed the Declaration of Helsinki Principles and formal consent was taken from participants before the survey.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: T.Ö.A., T.A., N.C., H.S., Concept: T.Ö.A. Design: T.Ö.A., T.A., Data Collection or Processing: T.Ö.A., N.C., H.S., Analysis or Interpretation: T.Ö.A., T.A., Literature Search: T.Ö.A., T.A., N.C., H.S., Writing: T.Ö.A., T.A.

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# The Frequency of Squamous Cell Carcinoma Among Patients with Long Standing Burn Scars

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## ABSTRACT

**Background:** Burn scar is a common complication of severe deep burns and its management could be started by medical therapy and or followed by plastic surgery. Squamous cell carcinoma (SCC) could result as consequence of long standing burn scar.

**Materials and Methods:** This case series descriptive study where a total of 172 patients with burn scars were seen during the period from 2014-2021. These patients were screened for cases with post burn scar SCC and the different triggering factors were evaluated. Biopsies for histopathological assessment were done.

**Results:** A total of 172 patients with burn scar, their ages ranged from 1-50 years with a mean 25 year, 122 (71%) males and 50 (29%) females. All had history of burn and the age of the scar was ranged from 0.5-5 years. Twelve (6.97%) cases of SCC were seen among all patients with burn scars, their ages ranged from 25-50 years with long standing burn scar. The sites of these cancers were as follow: 6 (50%) cases on lower limbs including the buttock, 5 (41.66%) cases upper limbs and one (8.33%) case on scalp. The associated triggering risk factors were male sex, deep burn scar with contracture, long duration, at the sites of flexures like elbows and knees. In addition to sites subjected to repeated trauma, ulcerations and infection.

**Conclusion:** The frequency of squamous cell among burn scars was 6.97%. All patients with deep burn scar should be watched carefully for burn SCC especially scars in male with frequent infection, ulcerations, repeated trauma and contracture around the joints. Early medical therapy is strongly indicated but if this maneuver fails then excision and grafting might prevent this important complication.

**Keywords:** Burn scar, Ulcer, Squamous cell carcinoma

## Introduction

A burn trauma is one of the most severe forms of injury to the skin and each year about 300,000 people die because of burns. Advancement in acute burn care has decreased mortality rate in the last few decades. After-burn injury, the prevalence of hypertrophic scarring is about 70% [1]. There are 2 varieties of scarring that follow burn trauma-keloid or hypertrophic scar.The period for the development of keloid usually ranged from months to years, while the hypertrophic scar usually appear 4-8 weeks post burn injury. keloid grow beyond the original defect while hypertrophic scar does not grow beyond the borders of the original defect [2,3].

Squamous cell carcinoma (SCC) is a most common post burn scar cancer that originates from the malignant proliferation of the keratinocytes [4,5]. In the etiopathogenesis, different factors such as thermal factors, arsenic, solar factors, immunosuppression, chronic radiation, and viral factors are responsible [5,6].

Malignant transformation of post-burned scars is an unavoidable probability. About 2% of ulcers and deep burns that had been

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healed by secondary intention, unstable post-burned scars that frequently ulcerate due to repeated petty traumatic insult and those which never healed completely, will develop malignant transformation. This finding is commonly seen in the lower limbs, especially around joints such as the knees [7,8,9]. So the aim of the present work is to record all cases of SCC following burn scars and to evaluate the triggering risk factors involved in its pathogenesis.

## Materials and Methods

This case series descriptive study where a total of 172 patients with burn scars were seen during the period from August 2014-January 2021. These patients were screened for cases with post burn scar SCC and the different etiological factors were evaluated. Biopsies for histopathological assessment using hematoxylin and eosin were done for every patient with chronic burn scar ulcers or any lesion with suspicion or features of malignant changes.

The diagnosis of SCC was made on the basis of history and clinical examination and confirmed by histopathological results.

Name, age, gender, onset of the burn, site of burn scar, site and nature of the ulcer, and the interval between primary burn injury and occurrence of SCC were recorded. For each patient: a full clinical examination was achieved in addition to complete systemic examination.

Oral consent was taken from each patient before starting the study. Close-up photographs were taken for each patient.

### Statistical Analysis

Statistical Package for the Social Sciences version 23 was used for data input and analysis. Data were statistically described in terms of mean, frequencies (no. of cases), male to female ratio and percentage (%).

## Results

A total of 172 patients with burn scar, their ages, ranged from 1-50 years with a mean 25 years, 122 (71%) males and 50 (29%) females with male to female ratio was 2.44:1. All had history of burns and the age of scar was ranged from 0.5-5 years. Twelve (6.97%) cases of SCC were seen among all patients with burn scars, their ages ranged from 25-50 years with a mean of 37.4 years and were 10 (83.33%) males and two (16.66%) females i.e. ratio of 5:1. The sites of these cancers were as follow: 6 (50%) cases on lower limbs including the buttock, 5 (41.66%) cases upper limbs and one (8.33%) case on scalp. The associated triggering risk factors were male sex, deep burn scar with contracture, long duration, at the sites of flexures like elbows and knees. In addition to sites subjected to repeated trauma, ulcerations and infection.

Two clinical kinds of post-burn SCC were encountered:

(i) The flat, ulcerative variety with raised margins was seen in 9 (75%) cases (Figures 1, 2, 3).

(ii) The nodular, fungating lesion was seen in 3 (25%) cases.

The mean of the interval between primary burn injury and occurrence of SCC was 3.5 years. The results of histopathological studies showed well-differentiated SCC (Figure 1B).

No metastasis to the regional lymph nodes or other parts of the body was recorded during clinical examination.

## Discussion

The mutagenic behavior with regular mitosis in regeneration and healing that usually follows burn scars represent the ultimate key mechanism initiating malignant transformation [8]. Although the definite pathogenesis of burn scar malignancy is not well known, multiple factors enhancing malignant transformation on burn scar have been defined. It is believed that repeated ulcers and healings particularly at the sites exposed for repeated trauma especially around joints can lead to malignant changes [10,11,12,13]. Chronic mechanical irritation, poor lymphatic regeneration, release of local toxins after burn injury, scar characteristics i.e. thickness, nutrition state, and degree of contraction are the other factors that may contribute burn scars to develop malignancy [11,13].

In multiple reports, the mean age for SCC arising in burn scars ranged from 36 years by Iregbulem [14], to 58.5 years by Arons et al. [15]. In the present work the mean age of SCC patients was 37.4 years, this finding falls within the range of previously reported studies [14,15].

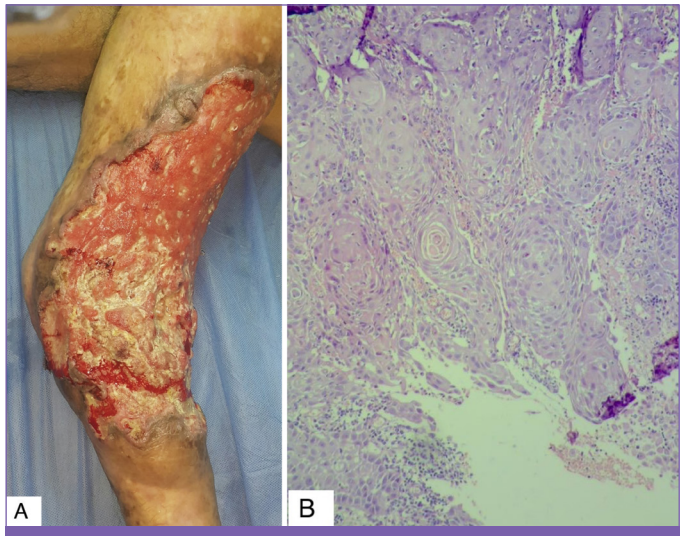


**Figure 1.** Thirty-five years old male with ulcerated squamous cell carcinoma arising within long standing burn scar on the left lower limb (A). Hematoxylin and eosin stained section of the same lesion showing hyperkeratosis well differentiated squamous cell carcinoma (B x10)

It has been reported that males are mostly affected by SCC arising in burn scars [14,16,17,18]. In the present study, 83.33% of our cases were males and this finding is comparable with these previous studies.

The frequency of SCC among all patients with burn scars, in the current study was (6.97%), this figure is comparable to one study [19] but slightly higher than other published works [20,21]. This finding is not surprising as sunny climatic condition during the whole year time and the early continuous sunlight exposure during outdoor activities in correlation with job time is more important for development of SCC [22].

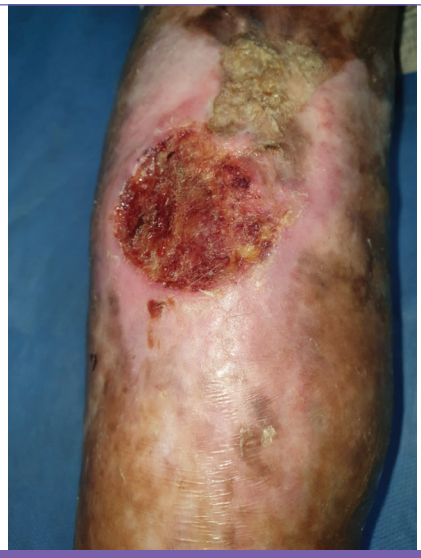

**Figure 2.** Twenty-eight years old male with post-burn squamous cell carcinoma of right leg

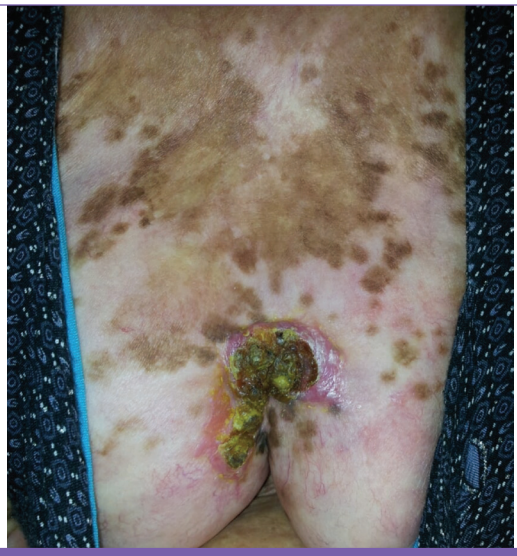

**Figure 3.** Twenty-five years old female with post burn squamous cell carcinoma on the buttock

Generally, SCC is mostly seen at the head/neck, while SCC arising on burn scars is frequently localized on lower extremities, where the trauma risk is high and the blood flow is low [16] in addition, the extremities are more susceptible to deep burns than other sites of the body. In the present work, 6 (50%) of 12 SCCs developing on burn scars were localized on lower extremities, 5 (41.66%) cases on the upper limbs and one (8.33%) case on the scalp. These results are in agreement with other studies [14,17,19].

The mean of the latent period of SCC patients in our study was 3.5 years which is shorter than other studies [14,17,19,18]. A possible reason behind this disparity may be differences in ethnicity and a long-term sunlight exposure among Iraqi population which can be a causative factor for earlier development of SCC.

SCC complicating a chronic burn scar is an unusual phenomenon. About 2% of the burn scars undertake malignant change to SCC, while 0.3-0.5% to basal cell carcinoma (BCC) [4,21]. In the present study, all of the cases had a malignant change to SCC. No BCC or malignant melanoma was recorded.

The most important strategy for the prevention of skin cancers is the prevention of burn injuries. Prevention of infection of the burned skin and avoidance of trauma to the burn scars are other steps for the protection against the development of skin cancers. Medical management for burn scars should be started as soon as possible to minimize scar formation and reduce scar size [23].

In case of suspicion of malignant transformation in the burn scar, biopsy for histopathological studies and follow up in regular times should be done. Surgical intervention should be performed as early as indicated in case of grafting, treatment of scar contracture and excision of any scar with suspicion of malignant features.

### Study Limitations

This study showing huge number of patients with well documented cases of SCC accordingly we think there is no limitation of the study.

## Conclusion

The frequency of SCC among burn scars was 6.97%. All patients with deep burn scar should be watched carefully for burn SCC especially scars in male with frequent infection, ulcerations, repeated trauma and contracture around the joints. Biopsy for pathological studies and follow-up to be done regularly in any ulcer of long standing burn scar to rule out any malignant transformation. Early medical therapy is strongly indicated but if this maneuver fails then excision and grafting might prevent this important complication.

### Ethics

**Ethics Committee Approval:** The study followed the Declaration of Helsinki Principles and it was approved by the Ethics Committee of Fallujah Teaching Hospital (approval number: 887, date: 17/6/2021).

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: K.E.S., R.I.J., Concept: K.E.S., R.I.J., Design: K.E.S., R.I.J., Data Collection or Processing: K.E.S., R.I.J., Analysis or Interpretation: K.E.S., R.I.J., Literature Search: K.E.S., R.I.J., Writing: K.E.S., R.I.J.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Dermatological Findings Observed After Renal Transplantation in Patients

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## ABSTRACT

**Background:** Renal transplant recipients tend to have a variety of skin diseases due to multiple immunosuppressive medications, accompanying co-morbidities and prolonged survival with the transplantation procedure. The aim of this cross-sectional study is to present dermatological findings and the contributing factors in renal transplant recipients.

**Materials and Methods:** Forty-one renal transplant recipients were examined by dermatologists between February and May 2021. The etiology of the chronic renal failure, the age at the time of the transplantation, time after transplantation, current medications, donor features, socio-demographic features of the patients, history of dialysis and accompanying co-morbidities were questioned.

**Results:** Average age of patients (27 male, 14 female) was 49.9±11.2 years. Average time after renal transplantation was 12.8±6.6 years. 87.8% of the patients were taking mycophenolate mofetil; 78% systemic steroids, 68.3% tacrolimus, 22% cyclosporin-A and 12.2% azathioprine. Skin signs due to immunosuppressive medications were more frequent in younger patients (p=0.031). Xerosis of the skin due to immunosuppressive medications was found in 41.5% and acneiform eruption in 34.1% of the patients. For skin infections, superficial fungal infections were the most frequent (73.2%), 56.1% of them being onychomycosis. Warts (22%) were the most frequent viral skin disease (31.7%). Viral and fungal skin infections were significantly more common in patients who are taking tacrolimus (p=0.024 and p=0.002, respectively). Fungal skin infections were more common in patients with prolonged and high-dose mycophenolate mofetil treatment (p=0.021 and p=0.005, respectively). Kaposi sarcoma was found in one of the patients and *in situ* squamous cell carcinoma was found in another patient. The most common oral lesion was gingival hyperplasia (29.3%).

**Conclusion:** Fungal and viral skin infections, skin cancers, acneiform eruptions, xerosis of the skin and gingival hyperplasia are commonly seen in renal transplant recipients. Therefore, proper dermatologic follow-up examinations are crucial.

**Keywords:** Renal transplantation, Xerosis, Acneiform eruption, Superficial fungal infections, Warts

## Introduction

Renal transplantation is the most ideal and efficient treatment option of end stage renal failure and severe chronic renal diseases, besides improving the quality of patients' lives [1]. However, immunosuppressive treatment which is usually necessary for lifetime to prevent the rejection of the transplanted kidney makes the patients prone to skin diseases like infections and non-melanoma skin cancers [2,3,4]. In addition, several accompanying comorbidities and prolonged life expectancy after transplantation increase this trend [5]. For these reasons, it is very important for the renal transplant recipients to undergo patients who have had

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kidney transplantation have regular follow-up for with dermatologic examinations. This is necessary not only to prevent the impact of possible dermatological diseases on the patients' quality of life but also to properly manage the complications that may occur.

The aim of this cross-sectional study is to review the skin diseases in renal transplant recipients and possible contributing factors that may affect them such as immunosuppressive medications, time after transplantation and donor characteristics.

## Materials and Methods

We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the Istanbul University Medeniyet Training and Research Hospital Local Ethics Committee (date: 13.01.2021, approval number: 0003). Forty-one patients who were being followed-up after kidney transplantation at the Nephrology Department of the Medeniyet Training and Research Hospital of the Istanbul University, and agreed to participate in the study were examined by dermatologists of the same hospital between February 1st and May 30th, 2021. Patients were questioned about their socio-demographic characteristics, age at the time of renal transplantation, disease that caused renal failure, donor characteristics, the type and duration of the immunosuppressive treatment, accompanying comorbidities and the history of dialysis. The patients provided written consent stating that they agreed to participate in the study.

### Statistical Analysis

The data obtained in the study were analysed with the Statistical Package for the Social Sciences IBM 25.0 package data program. Descriptive statistics (mean-standard deviation) and frequency distributions are presented. Independent group comparisons test statistics on continuous measurements were calculated by Mann-Whitney U test and binary group comparisons were calculated by chi-square test. The confidence level is set at 95%. A p value below 0.05 was considered significant.

## Results

### Socio-demographic Characteristics, Transplantation History and Accompanying Diseases of the Patients

A total of 41 patients participated in our study, 14 of whom were women and 27 of whom were men. The mean age of the patients was 49.9±11.2 years (21-70). The socio-demographic characteristics of the patients, the diseases that necessitated the transplantation, the time after transplantation, the characteristics of the donor and accompanying comorbidities are summarized in Table 1.

Of all the patients, 90.2% were treated with either peritoneal dialysis or haemodialysis before transplantation. Average duration of dialysis was 1.9±0.3 years. Two of the patients (4.9%) had admitted to the dermatology outpatient clinic while on dialysis. A patient was diagnosed with dermatofibroma, and the other one was treated for tinea pedis and corporis. Eight patients (19.5%) admitted to the dermatology department by themselves due to skin problems after transplantation. These patients were diagnosed with seborrheic keratosis, stasis dermatitis, zona zoster, irritant contact dermatitis, dermal nevus, macular drug eruption due to antidiabetic medications, genital warts and pityriasis versicolor. Thirty-four (82.9%) of the patients had accompanying comorbidities, hypertension being the most frequent one (53.6%), followed by diabetes mellitus (26.8%) and hypercholesterolemia (7.3%). Five patients (12.2%) had systemic cancers. Two had prostate cancer, 2 had papillary thyroid cancer and one had colon carcinoma.

### The Immunosuppressive Treatment and Skin Signs Associated with These Medications

The medications, doses and duration of the treatment of patients after renal transplantation are summarized in Table 2. For systemic treatment, 87.8% of patients were taking mycophenolate mofetil, 78% corticosteroids, 68.3% tacrolimus, 22% cyclosporin-A and 12.2% azathioprine.

Skin findings due to immunosuppressive drugs were observed in 85.4% of patients. These findings were more frequent in young patients. The mean age of those with skin findings was 48 years±11 years, while those without skin findings were 59 years±8 years (p=0.031).

Most commonly, 41.5% of patients had xerotic body skin followed by acneiform eruption in 34.1%, seborrhoea on the face in 31.7%, sebaceous gland hyperplasia in 24.4%, gingival hyperplasia in 22%, flushing in 17.1%, facial telangiectasia in 12.2%, demodicosis in 12.2%, striae in 9.8%, moon face in 7.3%, purpura in 7.3%, dorsocervical fat accumulation in 2.4% of the patients (Figure 1).

### Skin Infections

Superficial fungal infections were found in 73.2%, viral infections in 31.7%, parasitic (all cases demodicosis) in 12.1% and bacterial skin infections in 9.8% of the patients.

Fungal infections were more common as the time after transplantation was prolonged. The mean time after transplantation was 14±7 years in patients with fungal infections, while it was 9±4 years who did not have fungal infections (p=0.036). In addition, fungal infections were common in patients who were taking tacrolimus and mycophenolate mofetil for a longer period. Average duration of tacrolimus therapy was 98±99 months in patients with fungal infections, while it was 86±51 months in patients without fungal infection (p=0.002). For mycophenolate mofetil, average duration of therapy was 173±85 months in patients with fungal infections vs 72±77 months (p=0.021). Fungal infections

were also more frequent in patients who were on higher doses of mycophenolate mofetil (1135±487 mg/day vs 456±401 mg/day, p=0.005). For the distribution of fungal infections, onychomycosis of the feet was found in 48.8% of patients, onychomycosis of hands in 7.3% of, tinea pedis in 43.9%, pityriasis versicolor in 24.4%, tinea cruris in 2.4% and candida infections in 2.4% (Figure 2A, 2B). One of the patients had a history of deep fungal infection in the leg which had healed with scar formation.

Viral skin infections were more common in patients with longer duration of accompanying comorbidities (18±10 years vs 4±7 years, p=0.002). Of all patients on tacrolimus treatment, 57.1% had viral skin infections, while 42.9% did not (p=0.024). However, neither duration nor dose of tacrolimus were correlated with viral infections (p=0.822; p=0.219, respectively). Warts were the most common viral skin infection (22%) (Figure 2C). The most common location were feet (12.2%), followed by hands (9.8%), and other parts such as body and face (7.3%). Zona zoster was found on the leg of a patient. 12.2% of the patients had history of zona zoster with one of them recalcitrant postherpetic neuralgia. Active herpes simplex infection was found in 14.6% of patients (lips 9.8%, nose 4.9% and face 4.9%,

**Table 1. The socio-demographic characteristics, primary diseases, and information about renal transplantation of patients**

| | | Number | % |
|---|---|---|---|
| **Gender** | Female | 14 | 34.1 |
| | Male | 27 | 65.9 |
| **Marital status** | Married | 25 | 61.0 |
| | Single | 16 | 39.0 |
| **Age** | | 49.9±11.2 years | |
| **Education level** | Middle school and lower | 18 | 43.9 |
| | High school and higher | 23 | 56.1 |
| **Smoking status** | Smoker | 8 | 19.5 |
| | Non-smoker | 21 | 51.2 |
| | Ex-smoker | 12 | 29.3 |
| **Smoking pack year** | | 9.2±11.5 years | |
| **Alcohol consumption** | Regular | 1 | 2.4 |
| | None | 29 | 70.7 |
| | Social | 11 | 26.8 |
| **Are parents related** | No | 33 | 80.5 |
| | Yes | 8 | 19.5 |
| | Parents are sibling children | 2 | 4.9 |
| | Parents are cousin children | 6 | 14.7 |
| **Duration after transplantation** | | 12.8±6.6 years | |
| **Transplantation age** | | 38.4±10.9 years | |
| **Etiology of primer renal failure** | Immunoglobulin A nephropathy | 2 | 4.9 |
| | Hypertension | 7 | 17.1 |
| | Glomerulonephritis | 4 | 9.8 |
| | Alport syndrome | 2 | 4.9 |
| | Diabetes mellitus | 5 | 12.2 |
| | Infection | 11 | 26.8 |
| | Polycystic kidney disease | 5 | 12.2 |
| | Renal atrophy | 2 | 4.9 |
| | Vesicoureteral reflux | 2 | 4.9 |
| | Unknown | 1 | 2.3 |
| **Donor characteristics** | Stranger | 23 | 56.1 |
| | Consanguineous | 18 | 43.9 |
| | Brain death | 17 | 41.5 |
| | Live donor | 24 | 58.5 |

respectively). Of the patients, 43.9% had a history of recurrent herpes simplex infection (Table 3). Molluscum contagiosum was found on the arms of a patient (Figure 2D).

Folliculitis (7.3%) was the most commonly bacterial skin disease and paronychia of both toes was found in a patient.

### Malignant and Premalignant Lesions

Malignant and premalignant lesions were found in 26% of patients. Actinic keratosis and lentigo were seen in two patients and dysplastic nevus were seen in a patient. A patient was diagnosed with Kaposi's sarcoma which was located on the hand, foot and abdomen. *In situ* squamous cell carcinoma was found in one patient which was located on the back (Figure 3A). Two of the patients had a history of squamous cell carcinoma on the forehead and scalp which had been diagnosed previously.

### Nevi

Various types of nevi were found in 17.1% of patients. Four patients had dermal and compound nevi, two patients had congenital nevi and a patient had nevus sebaceous (Figure 3B). Nevi were common in elderly patients; average of patients with nevi was 59±13 years versus 48±10 years in patients who did not have nevi (p=0.011).

### Oral Lesions

Various oral lesions were detected in 53.7% of the patients. Oral lesions were more common in patients who were taking tacrolimus than those who did not (57.14% and 42.86%, respectively, p=0.042). Gingival hyperplasia was the most common lesion (29.3%), followed

**Table 2. Drugs usage due to kidney transplantation**

| Drugs | | Number (%) |
|---|---|---|
| Systemic corticosteroid | None | 9 (22) |
| | Yes | 32 (78) |
| | Duration (months) | 128.5±98.8 |
| | Dose (mg/day) | 3.9±2.6 |
| Tacrolimus | None | 13 (31.75) |
| | Yes | 28 (68.25) |
| | Duration (months) | 95.1±87.9 |
| | Dose (mg/day) | 1.9±1.6 |
| Mycophenolate mofetil | None | 5 (12.25) |
| | Yes | 36 (87.75) |
| | Duration (months) | 145.8±93.8 |
| | Dose (mg/day) | 948.5±553.1 |
| Azathioprine | None | 36 (87.8) |
| | Yes | 5 (12.2) |
| | Duration (months) | 12.3±38.1 |
| | Dose (mg/day) | 8.54±24.1 |
| Cyclosporin-A | None | 32 (78) |
| | Yes | 9 (22) |
| | Duration (months) | 47.7±96.8 |
| | Dose (mg/day) | 28.1±57.9 |

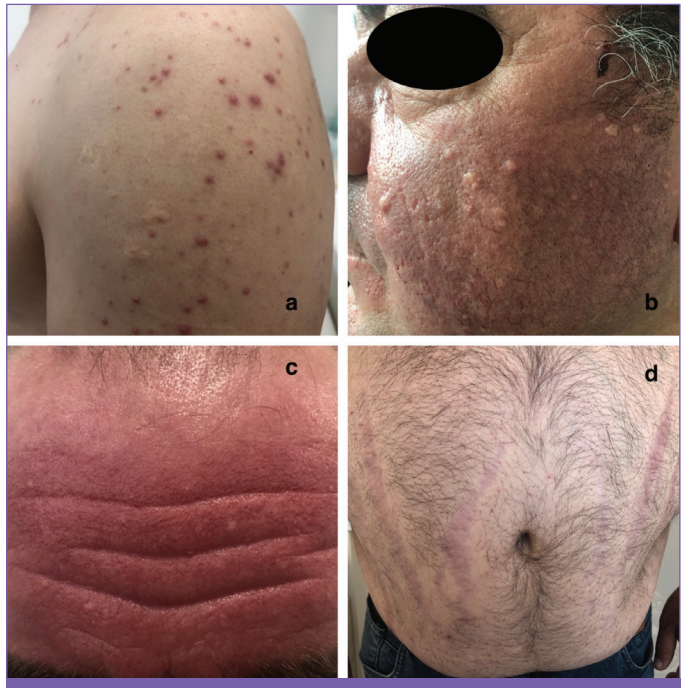


**Figure 1.** Skin findings of the patients due to immunosuppressive treatments. A) Acneiform eruptions on body. B) Seborrhoea, sebaceous gland hyperplasia, facial telangiectasia on the face. C) Flushing and facial telangiectasia on the face. D) Striae on the abdominal area

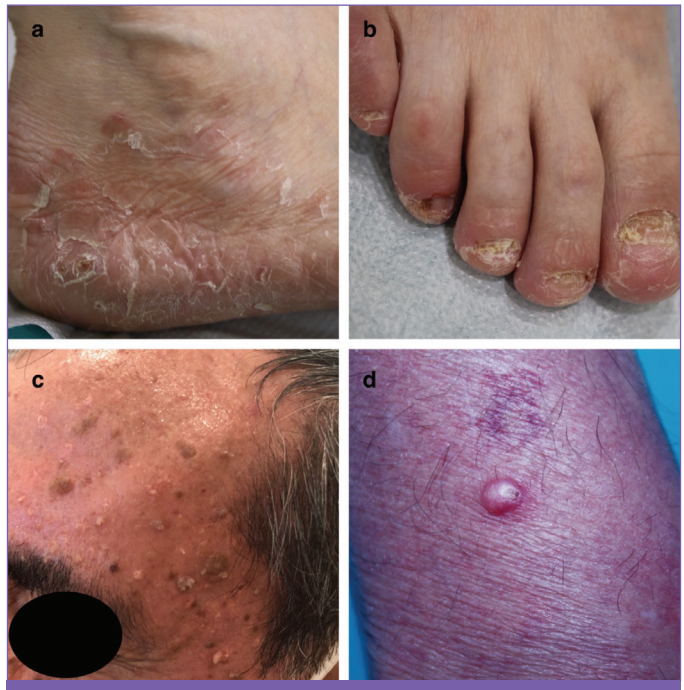


**Figure 2.** Skin infections of the patients. A) Tinea pedis. B) Onychomycosis on feet nails. C) Warts and also seborrheic keratosis on the face. D) Molluscum contagiosum on the arm

by atrophic glossitis (19.5%), hairy tongue (14.6%) and actinic cheilitis (4.9%) (Figure 3C).

### Other Skin Lesions

Other skin lesions found in patients are summarized in Table 4. These lesions were more frequent in patients who were older at the time of transplantation (39±11 years) than the younger ones (32±4 years) (p=0.038). They were also more frequent in elderly patients (60±9 years) than younger patients (48±11 years) (p=0.026). In addition, ephelides, contact dermatitis, vitiligo, nail discoloration, dermatofibroma, pincer nail, half and half nail, rosacea, milium cyst, splinter haemorrhage, lipoma, ganglion cyst and hypertrophy of the shunt area were detected in different patients (Figure 3D).

## Discussion

Our study has shown that patients with renal transplantation may have skin lesions and diseases of a varying spectrum, due to both the effects of the immunosuppressive medications and accompanying comorbidities. Dermatological side effects of the medications were more frequent in younger patients among which xerotic skin and acneiform eruptions were the most common ones.

**Table 3. History of recurrent herpes simplex infection**

| | | Number (%) |
|---|---|---|
| **History of herpes simplex** | None | 23 (56.1) |
| | Yes | 18 (43.9) |
| **Which part of the body** | Lips | 17 (41.5) |
| | Nose | 1 (2.4) |
| **Number of repetitions in a year** | | 3.1±2.6 |
| **Recovery time** | Days | 7.25±5.01 |
| **Duration of herpes simplex repetition** | Years | 16.9±7.1 |

**Table 4. Other skin findings detected in patients**

| Findings | Number (%) |
|---|---|
| Seborrheic keratosis | 11 (26.8) |
| Hyperpigmentation | 10 (24.2) |
| Acrochordon | 9 (22) |
| Ecchymosis | 4 (9.8) |
| Androgenic alopecia | 5 (12.2) |
| Pruritus | 4 (9.8) |
| Onychodystrophy | 4 (9.8) |
| Senile angioma | 4 (9.8) |
| Seborrheic dermatitis | 3 (7.3) |
| Telogen effluvium | 3 (7.3) |
| Onycholysis | 2 (4.9) |
| Unguis incarnatus | 2 (4.9) |
| Dermoid cyst | 2 (4.9) |

The most common infections were superficial fungal infections, followed by viral infections. While tacrolimus and mycophenolate mofetil increased the tendency to fungal infections, tacrolimus increased the tendency to viral infections, too. Tendency to fungal infections increases as the period after transplantation gets longer and tendency to viral infections increases with the duration of accompanying comorbidities. Renal transplant recipients are also prone to skin malignancies.

It is known that skin lesions are more common in renal transplant recipients compared to normal population [2,6,7]. Among these, skin infections especially fungal and viral infections, non-melanoma skin cancers, gingival hyperplasia, alopecia and hirsutism are reported to be most common ones [7,8].

Fungal skin infections are the most common skin infections in renal transplant recipients with reported rates of 18-68% [2,9,10,11]. Fungal infections were also the most common infection in our study with a slightly higher rate (73.2%). Tendency to fungal infections increased as the time after transplantation get prolonged. Most common fungal infection was onychomycosis (56.1%) in our study. Onychomycosis was reported at a similar rate by Sandoval et al. [12] (58%), while Kartal et al. [13] reported only 5.3%. Ghaninejad et al. [11] reported pityriasis versicolor in 35% of the patients as the most common fungal infection. Pityriasis versicolor was slightly less frequent in our study (24.4%). However, in the study by Kartal

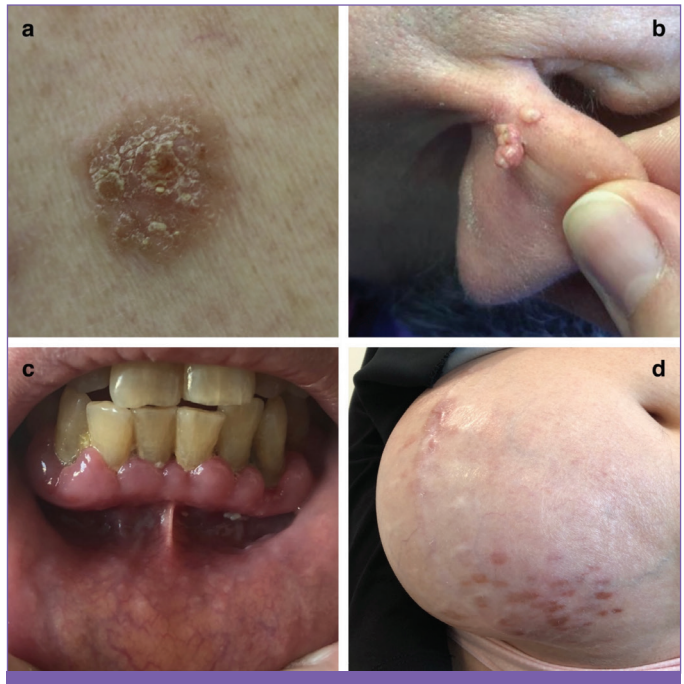


**Figure 3.** Different skin findings of the patients. A) *In situ* squamous cell carcinoma on the back of a patient. B) Nevus sebaceous on ear. C) Gingival hyperplasia. D) Hypertrophy of the shunt area on kidney seen on skin

et al. [13], this rate was 2.1%. Since superficial fungal infections are very common in society, it should be considered natural to see them frequently in renal transplantation patients undergoing immunosuppressive treatment as well.

Viral skin infections rates between 13-29.3% were reported among renal transplant recipients [2,10]. Warts were the most common viral infection in all studies. While the incidence of warts was reported between 15-32.3% in cross-sectional and retrospective studies, this rate increases to 92% in the follow-up cohort [5,7,13,14,15]. Although viral infection rates were slightly more frequent in our study (31.7%), warts (22%) were the most common one which is similar to the previous reports. Ghaninejad et al. [11] reported herpes infection in 34% of their cohort. Dymock [16] reported herpes simplex infection in 39% of patients in a retrospective analysis. Moloney et al. [7] reported recurrent herpes infection in 4.6% of the patients. Active herpes infection was found in 4.6% of patients in our study, however, 43.9% of patients had a history of recurrent herpes infection. The relatively less rate of active herpes infection in our study may be attributed to the cross-sectional nature. However, the rate of recurrent herpes infection history was similarly high. The higher rates of both warts and herpes infections are associated with immunosuppressive treatments.

Rate of bacterial skin infections were not frequent in our study (9.8%), but acneiform skin lesions were considered among bacterial infections in some studies. The rate of acneiform eruptions was 34.1% in our study. This rate has been reported between 17-60% in previous studies [2,11]. It is quite natural to find acneiform lesions which are an expected side effect of systemic corticosteroid treatment in renal transplant recipients who depend on low dose systemic corticosteroids nearly lifelong.

Malignant and premalignant skin lesions are more common in renal transplant recipients. Skin cancer rates were reported to be between 4.7-35% in the published studies [7,12,15]. Malignant and premalignant lesions were found in 26% of patients with a skin cancer rate of 4.8% in our study. However, 9.8% of our patients had a history of previously diagnosed skin cancer after transplantation. Renal transplantation patients should be monitored regularly in terms of skin cancers that are found more commonly than society. In addition to these findings, xerotic skin (41.5%), seborrhoea and sebaceous gland hyperplasia (31.7%; 24.4%, respectively) and gingival hyperplasia (22%) were also noted. Rate of xerotic skin was slightly lower in previous studies (2.1-33%) in comparison to our study [2,7,10,13]. This difference can be explained by the fact that our patients are prone to xerosis due to slightly older age compared to previous studies. Moloney et al. [7] reported sebaceous gland hyperplasia in 17.3% of patients. This rate, which was 24.4% in our study, was more commonly found in patients who had been taking cyclosporin-A for a long time. Gingival hyperplasia is noted as the most common oral lesion in many studies. However, Kartal et al. [13] and Engin et al. [2] have not observed gingival gland hyperplasia at all. The incidence of gingival hyperplasia was reported between 1.9-44% in previous studies, compared to 22% in our study [11,16,17,18]. Gingival hyperplasia has also been found more frequently in patients taking cyclosporin-A.

### Study Limitations

The limitation of our study is that it was carried out with relatively few patients due to the circumstances of Coronavirus disease-2019 pandemic. More studies are needed with a greater number of patients who are followed up for a longer period.

## Conclusion

Renal transplant recipients are particularly prone to fungal skin infections such as onychomycosis, viral skin infections such as warts and life-threatening skin cancers. In addition, acneiform eruptions, xerotic skin, sebaceous gland hyperplasia and gingival hyperplasia are also common due to the immunosuppressive medications. Therefore, it is very important to carry out regular dermatological follow-up for renal transplant recipients to prevent possible comorbidities and to enable proper and timely interventions.

### Ethics

**Ethics Committee Approval:** We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the Istanbul University Medeniyet Training and Research Hospital Local Ethics Committee (date: 13.01.2021, approval number: 0003).

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.A.K., H.A., Concept: M.A.K., H.A., Design: M.A.K., S.A.E., N.A., Data Collection or Processing: M.A.K., S.A.E., H.A., Analysis or Interpretation: M.A.K., S.A.E., Literature Search: M.A.K., H.A., Writing: M.A.K., N.A.

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CASE REPORT

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# Treatment of Two Patients with Erythrodermic Psoriasis with Ixekizumab During COVID-19 Pandemic

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## ABSTRACT

Erythrodermic psoriasis (EP) is the most severe form of psoriasis. Here, we report two cases of EP who achieved Psoriasis Area and Severity Index (PASI) 100 with the treatment of ixekizumab during Coronavirus disease-19 (COVID-19) pandemic. A female and a male patient with EP applied to dermatology outpatient clinic of our hospital. Treatment with standard dose ixekizumab (160 mg sc at week 0 and then 80 mg sc every 2 weeks for 12 weeks) led to PASI 100 response in our first case after only 5 weeks and in our second case after 6 weeks. To date, there have been six patients with EP who reached PASI 100 with ixekizumab treatment, one of them could achieve to this level earliest at week 6, one of them earliest at week 8 and four of them earliest at week 12, whereas our first case reached PASI 100 at week 5 and our second case reached at week 6. Our cases were deemed worthy of presentation because our female patient was the case with the fastest response to PASI 100 with ixekizumab, and our two cases were the first reported patients who reached PASI 100 during COVID-19 pandemic. Our patients continue ixekizumab treatment without any side effects and remain self-isolated at home.

Keywords: Psoriasis, Erythrodermic psoriasis, Ixekizumab, COVID-19

## Introduction

Psoriasis, with a worldwide prevalence of 0.5% to 3%, is a systemic inflammatory disease [1,2]. Erythrodermic psoriasis (EP) is the most severe form of psoriasis [3]. A recent class of biologic agents that has been approved for the treatment of moderate to severe psoriasis is the interleukin (IL)-17 inhibitors, which include secukinumab, brodalumab, and ixekizumab [4]. Ixekizumab is a recombinant, high affinity and humanized monoclonal antibody IgG that inhibits IL-17A [1,3]. There are few case series with EP who became better or treated completely with ixekizumab [2,5,6]. Here, we report two cases of EP who achieved Psoriasis Area and Severity Index (PASI) 100 with the treatment of ixekizumab during Coronavirus disease-19 (COVID-19) pandemic.

## Case Reports

### Case 1

A 31-year-old female with EP applied to the dermatology outpatient clinic of our hospital in March 2020. The patient was suffering from plaque-type psoriasis for 18 years. When referring to our clinic, she was affected by an erythrodermic form of psoriasis (Figure 1A, 1B). We learned that she became EP the second time and both first and second EP occurred after her pregnancy. She did not have another disease. PASI was 39.8 at baseline. We began ixekizumab for her on March 23, 2020. We said her that she should be isolated at home because of the COVID-19 outbreak during ixekizumab treatment. Treatment with standard dose ixekizumab (160 mg sc at week 0 and then 80 mg sc every two weeks for 12 weeks) led to PASI 90 response

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after only two weeks. Then, we observed a PASI 100 response to continuing at the patient's fifth-week control (Figure 2A, 2B). No adverse effects developed and until today no relaps have been observed. The patient's consent was obtained for this case study.

### Case 2

A 66-year-old male with EP applied to the dermatology outpatient clinic of our hospital in May 2020. The patient was suffering from plaque-type psoriasis for eight years. When referring to our clinic, he was affected by an erythrodermic form of psoriasis (Figure 3A, 3B). He had primary hypertension. PASI was 54 at baseline. We began ixekizumab for him on May 14, 2020. We said him that he should be isolated at home because of the COVID-19 outbreak during ixekizumab treatment. Treatment with standard dose ixekizumab (160 mg sc at week 0 and then 80 mg sc every two weeks for 12 weeks) led to PASI 100 response after only six weeks (Figure 4A, 4B). No adverse effects developed and until today no relaps have been observed. The patient's consent was obtained for this case study.

## Discussion

The first case with COVID-19 was recorded on March 11, 2020, in Turkey. Data on the EP of ixekizumab approved for the treatment of moderate to severe plaque psoriasis have been very limited to date. Megna et al. [3] presented a case with EP who healed with ixekizumab that was able to lead to a complete resolution of the disease after six weeks. In Saeki et al.'s [2] study, 100.0% of the EP patients achieved PASI 75, 62.5% (5/8) achieved PASI 90 and 25.0% (2/8) achieved PASI 100 at week 12 and 100.0% of the patients maintained PASI 75, 87.5% (7/8) patients achieved PASI 90 and 12.5% (1/8) patients achieved PASI 100 at week 24. In another study of Saeki et al. [7], it was presented that for eight patients with EP, global improvement scores indicated that all patients either

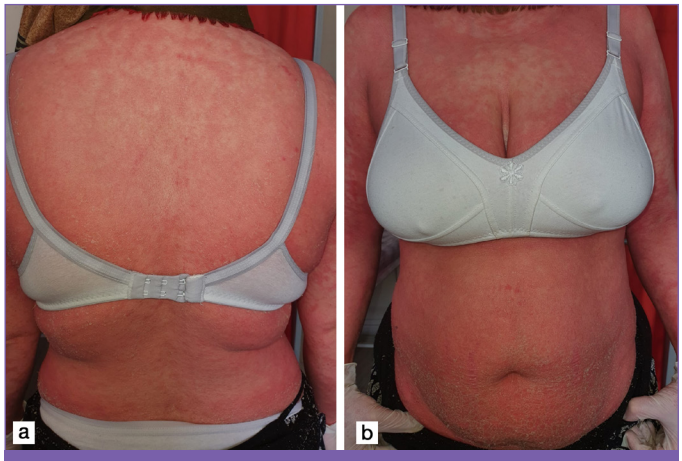


**Figure 1.** A) Diffuse erythem on the back. B) Diffuse erythem and desquamation in the front of the body

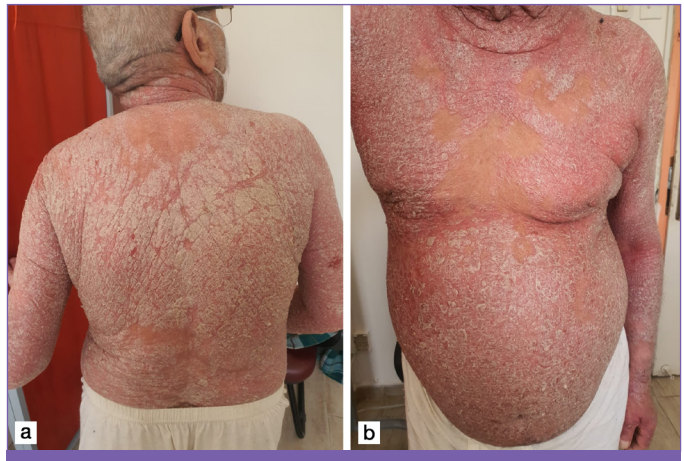


**Figure 3.** A) Diffuse erythem, desquamation and squams on the back. B) Diffuse erythem, desquamation and squams on the front of the body

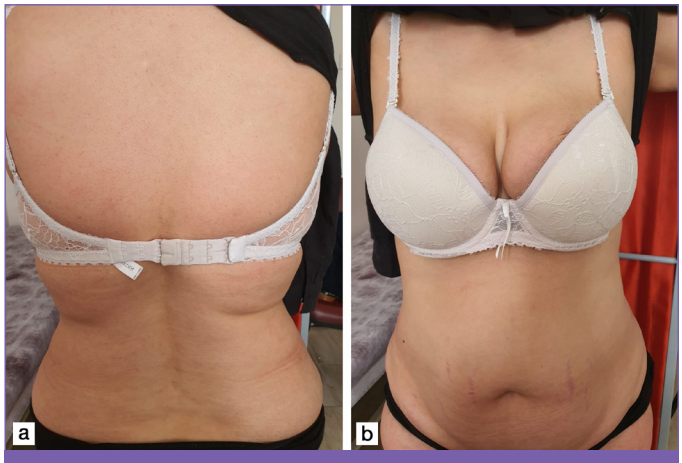


**Figure 2.** A) Normal skin of the back after healing. B) Normal skin of the front of the body after healing

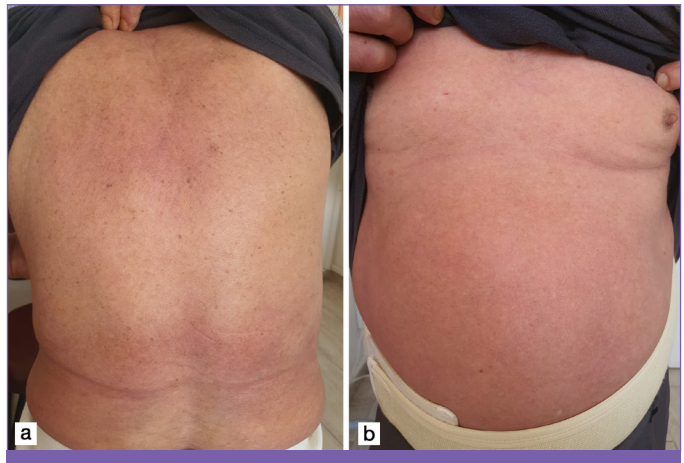


**Figure 4.** A) Normal skin of the back after healing. B) Normal skin of the front of the body after healing

resolved or improved by week 52 of the ixekizumab treatment. Improvements in PASI were observed at 12 weeks and maintained for the 52-week treatment period. All patients with EP responded (improved or resolved) to ixekizumab treatment. At week 52, six of the eight patients with EP reached PASI 90 response. In Carrasquillo et al.'s [5] study, eight patients were treated with ixekizumab as part of an open-label study. By week 12, all patients achieved PASI 75, 5/8 achieved PASI 90, and 2/8 achieved PASI 100. By week 24, 100% of the patients reached PASI 75, 7/8 reached PASI 90, and 1/8 reached PASI 100. After 52 weeks of follow-up, ixekizumab achieved significant improvement. According to this research, ixekizumab can be considered first-line treatments for EP. In Lo and Tsai's [6] study, at week 12, seven (78%) patients (total nine patients) achieved PASI 50; of these, four (44%) patients one (11%) patient achieved PASI 75 (75% reduction in PASI) and PASI 90 (90% reduction in PASI), respectively. The patient who achieved PASI 90 actually achieved PASI 100 at weeks 8 and 12. Okubo et al. [8] presented in their study that all eight patients had early and sustained improvement in PASI scores with ixekizumab treatment. In their research, the mean PASI score was 42.8 at baseline, 3.0 at week 52, and 5.0 at week 244. None of the patients with EP reached PASI 100. It was not explained in detail that how many patients reached PASI 50-75-90, but according to mean PASI score at week 52, there were few patients who reached PASI 90 response.

According to some studies, biologics were used safely during the COVID-19 pandemic. In Gisondi et al.'s [9] study, their findings showed that there was not a significant number of hospitalizations or deaths from COVID-19 (a multicentric study, 5206 cases with chronic plaque psoriasis being treated with biologic therapy). In another study conducted by Gisondi et al. [10], it was observed that among 980 patients with chronic plaque psoriasis on biologics, there were no cases of hospitalization or death. Additionally, a case from Italy who was 55 years old had contacted a COVID positive patient on his induction stage with ixekizumab, and then, he was tested for Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) resulted positive. He did not provide his doctors with this information and continued to use ixekizumab. His control test for SARS-CoV-2 resulted in negative, and in this process, he confirmed never having suffered from cough, dyspnea, anosmia, ageusia, myalgia or any other symptom of the infection. Interestingly, the IL-23/IL-17 axis does not seem to be pivotal in an effective immune response [11]. On the contrary, observations carried on both Coronavirus, and non-Coronavirus pneumonia patients show that an aberrant Th17 polarization may correlate with a worse outcome. Based on these observations, a clinical trial investigating the use of ixekizumab associated with antiviral therapy is currently ongoing in China as a possible treatment for COVID-19 infection. During COVID-19, inflammatory cytokines play a double role. Firstly, they stimulate effective immune response activation and then can mediate the development of exaggerated systemic inflammation. This cytokine storm is not effective on the pathogen of COVID-19 [12]. The outcome of data from currently available literature suggests that IL-23/IL-17 axis inhibition may not be detrimental in the setting of COVID-19 infection. Further data are needed to support this hypothesis.

To date, there have been six patients with EP who reached PASI 100 with ixekizumab treatment, one of them could achieve to this level earliest at week 6, one of them earliest at week 8 and four of them earliest at week 12, whereas our first case reached PASI 100 at week 5 and our second case reached at week 6. Our cases were deemed worthy of presentation because our female patient was the case with the fastest response to PASI 100 with ixekizumab, and our two cases were the first reported patients who reached PASI 100 during COVID-19 pandemic. Our patients continue ixekizumab treatment without any side effects and remain self-isolated at home.

### Ethics

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.G., D.D.B., Concept: M.G., D.D.B., Design: M.G., D.D.B., Data Collection or Processing: M.G., D.D.B., Analysis or Interpretation: M.G., D.D.B., Literature Search: M.G., D.D.B., Writing: M.G., D.D.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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CASE REPORT

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# Cutaneous Nodules as an Initial Manifestation of Neuroendocrine Carcinoma with Unknown Primary Site: A Case Report

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## ABSTRACT

Neuroendocrine tumors are heterogenous group of neoplasms arising from cells of neuroendocrine origin. They have a wide spectrum of clinical behavior and malignant potential. Cutaneous metastases of these tumors have been reported very rarely. We report a patient diagnosed with metastatic neuroendocrine carcinoma after a biopsy was performed from his skin nodules. Cutaneous nodules were one of the first manifestations of his internal malignancy and helped us to diagnose and manage the patient.

Keywords: Neuroendocrine tumor, Cutaneous metastasis, Cancer of unknown primary

## Introduction

Neuroendocrine tumors are rare neoplasms arising from cells of neuroendocrine origin. These tumors commonly originate from gastrointestinal tract, pancreas, lung, thymus and other endocrine organs [1]. They most commonly metastasize to lymph nodes, liver and lung [2]. However, cutaneous metastases of these tumors are very rare. In this article, we present a patient diagnosed with neuroendocrine carcinoma after his cutaneous nodules appeared. His cutaneous findings were one the first manifestations of his underlying malignancy.

## Case Report

A 72-year old man visited our clinic with multiple nodules on his trunk. He had a history of jaundice, malaise and weight loss for 3 weeks. His cutaneous nodules first appeared on right subclavicular area, followed by 4 new nodules on trunk within 1 week. Nodules were rapidly enlarging, but he did not describe any symptoms. He was brought to emergency department with intractable jaundice and constitutional symptoms a few days ago. Hepatobiliary ultrasonography was performed. In the head of pancreas; 2.5-cm sized, hypoechoic mass containing cystic, necrotic areas was observed.

The patient was directed to oncology department and malignancy work-up has been started. He was consulted to our dermatology department for diagnosis of cutaneous nodules. In the dermatologic examination; painless, firm, dome-shaped, red-purplish five discrete nodules were present on right subclavicular area, abdomen and right lateral site of thorax (Figure 1, 2). A biopsy was taken from the lesions, monomorphic, atypical small cells with round, hyperchromatic nuclei were seen in subcutaneous tissue with hematoxylin and eosin staining (Figure 3). Tumor cells were stained positive with chromogranin, synaptophysin, CD56 and thyroid transcription factor-1 (TTF-1) (Figure 4, 5); but negative with CK7, CK20, CD45, CDX2. Immunohistochemical staining features of cells were compatible with metastatic neuroendocrine carcinoma. Ki-67 proliferation index was studied and more than 95% proliferative activity was reported (Figure 6).

Further diagnostic tests were initiated to detect the primary tumor. In his thoracoabdominal computed tomography (CT); 12x10 cm

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Received: 23.02.2021 Accepted: 08.03.2021

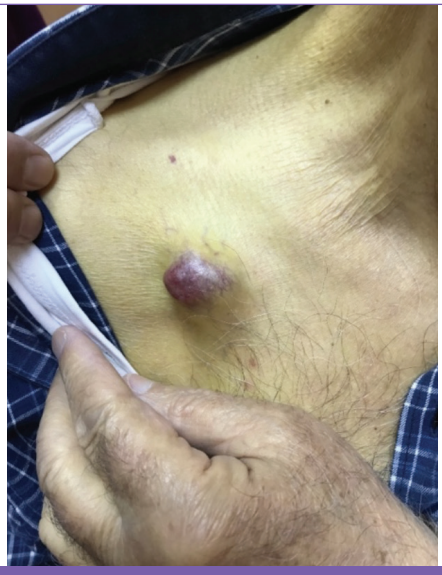

**Figure 1.** A firm, painless, 3x2-cm sized, purple nodule on the right subclavicular area

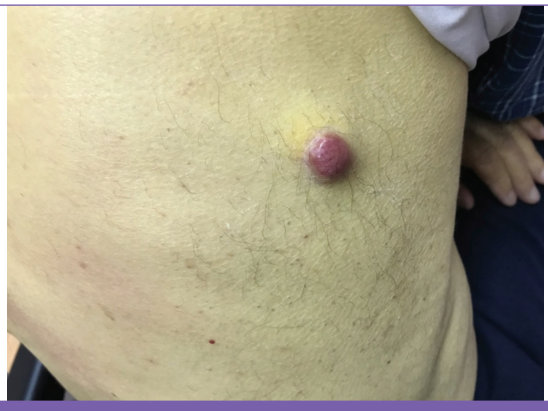

**Figure 2.** A painless, smooth-contoured, round-shaped, 2x2-cm sized red-purple nodule on the right lateral site of thorax

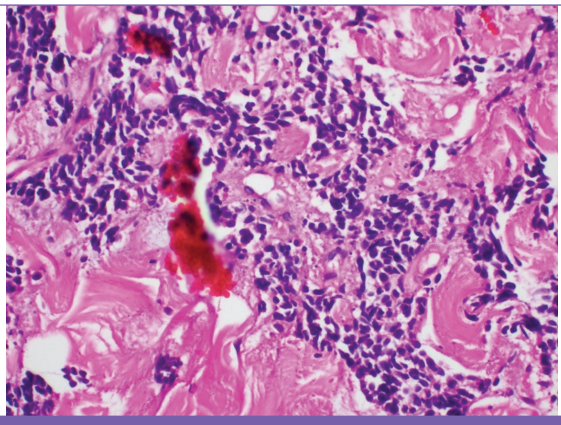

**Figure 3.** Monomorphic, atypical small cells with round, hyperchromatic nuclei in subcutaneous tissue are seen in hematoxylin and eosin staining

sized, lobulated mass containing cystic and necrotic areas was observed in the right lung parenchyma. The mass was obliterating right main bronchus and invading right middle and inferior lobe arteries. Tumoral masses were also observed in head and neck of pancreas and adrenal glands in CT. Thoracentesis was performed, but atypical cells were not observed. Endoscopic retrograde

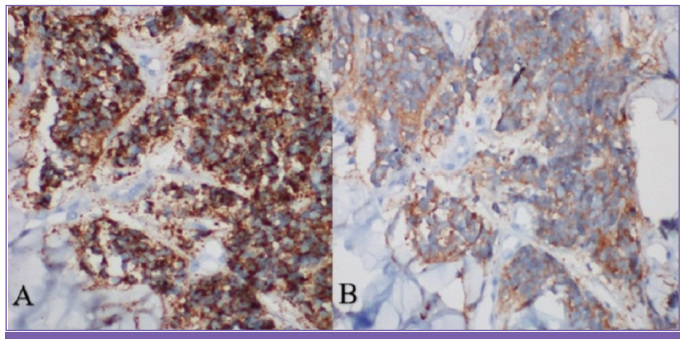


**Figure 4.** Immunohistochemical features of tumor cells. Tumor cells are immunoreactive with (A) chromogranin and (B) synaptophysin

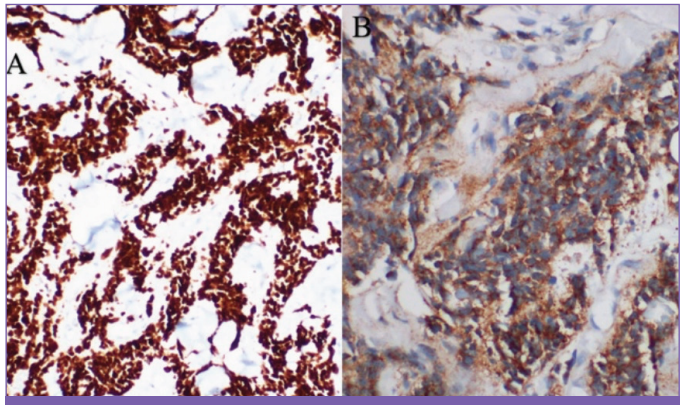


**Figure 5.** Immunohistochemical features of tumor cells. Tumor cells are immunoreactive with (A) thyroid transcription factor-1 (SP141 clone) and (B) CD56

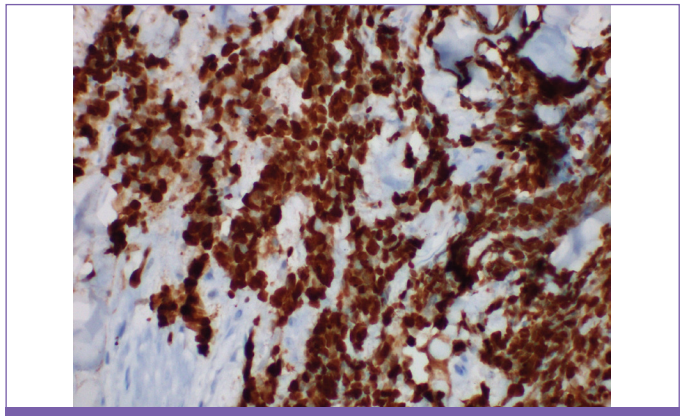

**Figure 6.** Tumor cells are stained diffusely positive with Ki-67

cholangiopancreatography (ERCP) procedure was performed by gastroenterologists. During ERCP, a biopsy was taken from ampulla of Vater; but neuroendocrine tumor or a tumor with epithelial origin could not be detected histopathologically. The exact location of primary tumor was still being investigated; etoposide/cisplatin chemotherapy has been started for metastatic neuroendocrine tumor.

## Discussion

Neuroendocrine tumors consist of heterogenous group of neoplasia originating from neuroendocrine cells throughout the body. They most commonly arise from gastrointestinal tract and bronchopulmonary system [3]. Their clinical presentation, tumor biology and metastatic potential vary widely. Different from their common metastatic sites-liver, lung or lymph nodes; cutaneous metastases of these tumors are very rare. Up to date, less than 40 cases with neuroendocrine tumor metastases to skin were reported [4]. Five of them had no systemic symptoms, presented only with cutaneous findings [4].

Contrary to patients who were diagnosed with neuroendocrine tumor and cutaneous findings arising later during their follow-up, or asymptomatic patients presenting only with cutaneous findings who were diagnosed with neuroendocrine tumor later; our patient's systemic and cutaneous findings emerged simultaneously. Dermatologic examination and histopathologic evaluation of his skin nodules played an important role in the diagnosis and management of the patient.

Merkel cell carcinoma, highly aggressive primary neuroendocrine carcinoma of skin, should be distinguished from metastatic neuroendocrine tumors. CK20 positivity and TTF-1 negativity are important features of Merkel cell carcinoma [5]. In our patient, CK20 staining was negative but TTF-1 staining was positive. His immunohistochemical and radiological findings, together with clinical signs and symptoms, were consistent with metastatic neuroendocrine tumor rather than Merkel cell carcinoma.

Cutaneous manifestations of neuroendocrine tumor metastases vary. Single or multiple, non-ulcerated, painless nodules are the most common manifestation [6]. Rarely, painful metastatic lesions were reported in the literature [7]. Our patient presented with multiple, painless, firm, red-purplish nodules. His systemic symptoms occurred 1 week after his skin nodules. Considering his systemic symptoms and imaging findings, underlying systemic malignancy was likely. His nodules became a practical location for biopsy and diagnosis of neuroendocrine carcinoma was confirmed. This case report is a rare example of neuroendocrine tumor metastasis to skin.

Neuroendocrine tumors rarely metastasize to skin, but their cutaneous findings might be the first manifestation of underlying malignancy. Clinical suspicion and histopathologic examination are important for these rare tumors. Dermatologists play important role in such cases and multidisciplinary approach is important in the management of these patients.

### Ethics

**Informed Consent:** Informed consent was filled out by all participants.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.E.T., Concept: M.E.T., Design: M.E.T., E.A., Data Collection or Processing: M.E.T., C.B.Ö., Analysis or Interpretation: M.E.T., C.B.Ö., E.A., Literature Search: M.E.T., C.B.Ö., E.A., Writing: M.E.T., C.B.Ö., E.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Tele-Patch: Inevitable Consequence of the Pandemic

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Keywords: Tele-patch, COVID-19, Patch test, Teledermatology, Case report

**Dear Editor,**

Telemedicine tools are viewed as essential and safe tools to improve the delivery of health services and become increasingly popular especially during the Coronavirus disease-2019 (COVID-19) pandemic. The principle aim of their use is to reduce and limit the number of face-to-face visits to hospitals thereby prevent the spread of the virus. Allowing quarantined COVID-19 patients to be given dermatologic consultation points to another benefit of the telemedicine applications [1]. Although the use of teledermatology for patch testing is not a new entity, it is limited to consultation of the photographs of patients whose patch tests are photographed in clinics to dermatologists by Store-and-Forward technology [2]. Herein we present a patient whose patch test was evaluated via teledermatology method because he was quarantined due to COVID-19 on the day of the patch test.

A 45-year-old male patient applied to the outpatient clinic with contact dermatitis in the hands. Since the patient's complaints responded partially to topical corticosteroid, a patch test was planned at the control examination. The patch test with a standard series of 30 allergens was applied to the patient's back, and the patient was called back to the hospital for the 48$^{th}$ and 72$^{nd}$-hour test readings. The patient was quarantined due to the diagnosis of COVID-19 in his mother and sibling on the day of the patch test, so the 48$^{th}$ (Figure 1) and 72$^{nd}$ (Figure 2A) test results of the patient was evaluated through the photographs sent by the patient using the mobile phone. The patch test result of the patient was evaluated as a 2+ reaction with potassium dichromate 0.5% (Figure 2B) and cobalt chloride hexahydrate 1.0% (Figure 2C), and detailed information about the allergens was sent to the patient via e-mail.

Although the combination of vision and palpating the induration is necessary for evaluating the results of the patch test, in a study in which the patch test results of the patients were evaluated only with photographs, only 6% failure was detected [3]. Spanish Contact

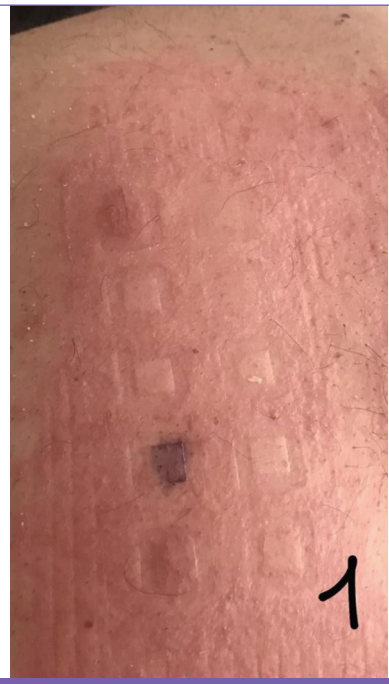


**Figure 1.** 48$^{th}$-hour photograph of the standard serial patch test with 30 allergens

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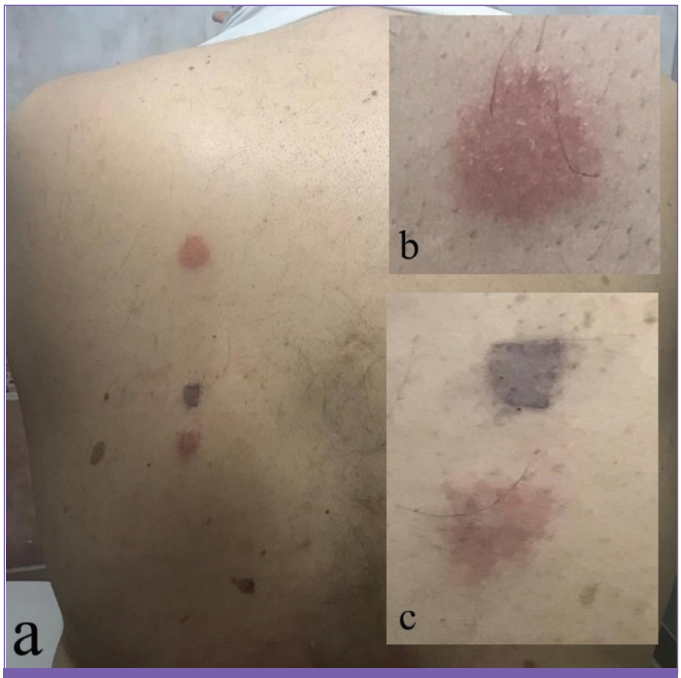


**Figure 2.** A) 72nd-hour photograph of the patch test with 30 allergens, close view of 2+ reaction with potassium dichromate 0.5% (B) and cobalt chloride hexahydrate 1.0% (C)

Dermatitis and Skin Allergy Research Group has proposed that patch test reading can be done in COVID-19 pandemic on photographs sent by patients in exceptional circumstances [3]. The virtual evaluation of patch test results is easy if there is negativity in the whole series, but weak positivity and irritant reactions can be confusing sometimes for dermatologists. Due to the image quality of the photographs is not always perfect, and difficulty for assessment without palpation of erythema, subtle edema, and vesiculation, virtual evaluation of photographs submitted by patients seems difficult to replace face-to-face evaluation. On the other hand, in exceptional cases, such as our patient, the patient's patch test can be read with a Store-and-Forward teledermatology using technological tools.

### Ethics

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Concept: A.S.K., Design: E.A., Data Collection or Processing: E.A., Analysis or Interpretation: A.S.K., Literature Search: A.S.K., Writing: A.S.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Basal Cell Carcinoma Originating from a Posttraumatic Scar at the Intergluteal Sulcus

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**Dear Editor,**

Basal cell carcinoma (BCC) is the most skin tumour. Chronic sun exposure is considered as the main etiologic factor in its development. We report a patient with perianal BCC which developed after trauma.

A 73-year-old woman presented with a one-year history of an erythematous ulcer on her intergluteal sulcus. The skin lesion grew gradually, but did not cause pain, bleeding or gastrointestinal symptoms. Her past medical history included hypertension, insulin-dependent diabetes mellitus and significant fall from the stairs five years ago on the ulcer site with a large wound that healed with secondary intention.

On examination, a single 4×4 cm, erythematous, asymptomatic ulcer with raised borders was observed in the intergluteal sulcus. A diagnostic punch biopsy was performed from the margin of the erosion. Histopathologic analysis demonstrated an ulcerated tumour within the dermis, composed of islands of basaloid cells, with palisading of the cells at the periphery. The tumour displayed an infiltrative pattern of growth. Besides the infiltrating type, micronodular and multifocal superficial types were also evident. These findings were consistent with mixed type BCC and total excision was suggested for treatment (Figure 1a, 1b). Computed tomography of the pelvis demonstrated an old fracture with subluxation at the sacrococcygeal joint. There were fuzzy amorphous densities showing posttraumatic soft fibrotic tissue (Figure 2). There were no evidence of metastatic disease. Local wide resection was performed with an intraoperative margin evaluation. The defect was closed with a Limberg flap (Figure 3a, 3b, 3c). Histopathologic examination of the total excision material was also found to be consistent with mixed type BCC. The surgical resection margin was free of malignant cell involvement. Complications or recurrences were not noted during the follow- up period.

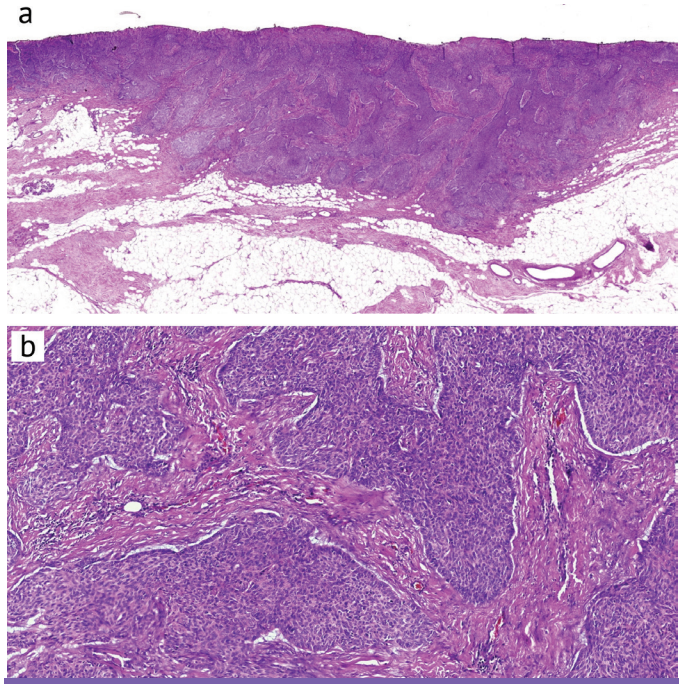


**Figure 1.** a, b) Islands of basaloid tumour cells with peripheral palisading [hematoxylin and eosin (HE) x20, HE x200]

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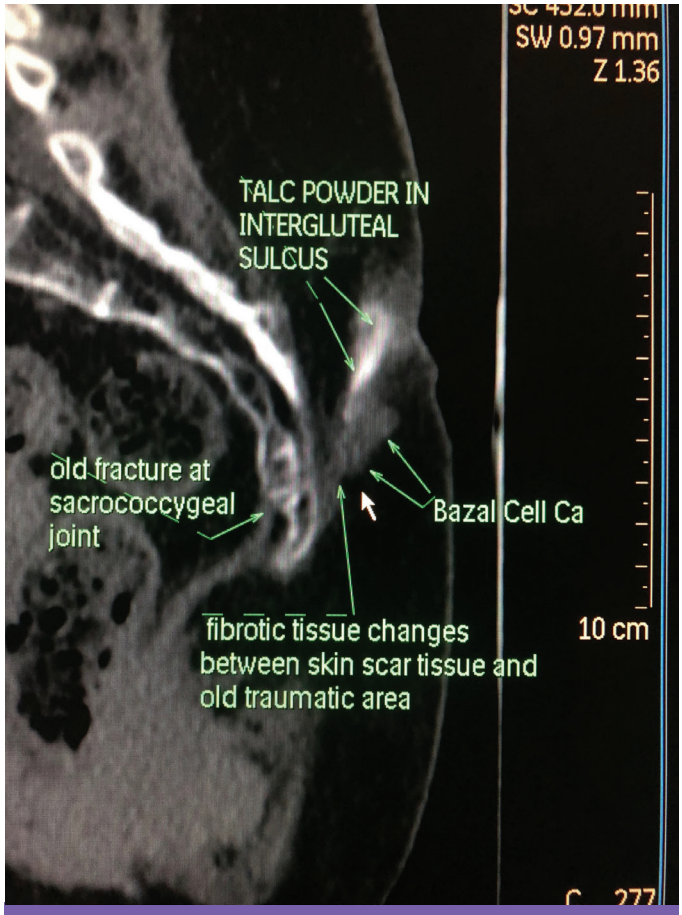


**Figure 2.** Sagittal computed tomography of the pelvis: Irregularities between skin scar tissue and old traumatic area (arrow), basal cell cancer (double arrow), old fracture at sacrococcygeal joint (stars), talc powder on the intergluteal sulcus (triple arrow)

BCC rarely occurs in the anogenital region among older individuals [1]. It varies from erythematous papules and patches to nodules, plaques, and ulcers with bleeding, discomfort, itching, and mucoid discharge. Our patient had an erythematous ulcer without symptoms. The etiology of perianal BCC remains unknown. Chronic irritation, trauma, immunosuppressive medications, radiation and scars are reported causative factors [2].

Scar tissue-related BCC is rare, but BCC can develop from nonhealing wounds, keloid tissues and previous surgical or vaccination scars. Healing by secondary intention is the most important risk factor in scar tissue-related BCC [3]. Our patient's wound healed by secondary intention. The pathogenesis of malignancy accompanied by trauma is vague. Chronic irritation, depressed cellular immunity, misplacement of epithelial cells, and tumour suppressor gene mutations have been identified as etiological factors for BCC in scar tissues. Mixed type BCC is an aggressive form of the tumour. This is prone to recurrence and develops mostly in the face and scalp [4]. The histopathological examination showed mixed type tumour and localised at the perianal area. A wide resection was performed. Arons et al. [5] proposed the following criteria to show the correlation between trauma and BCCs a) severe injury, b) normal skin integrity and absence of tumour before trauma, c) tumour related to the site of trauma or originating within boundaries of the injury, d) reasonable latent period, and e) tumour compatible with scar tissue. Our patient had a history of trauma on the tumour site with a wound that healed with secondary intention. Before the fall, she did not have BCC and notable risk factors.

This case illustrates the importance of long-term monitoring of areas not exposed to sunlight following trauma among older persons.

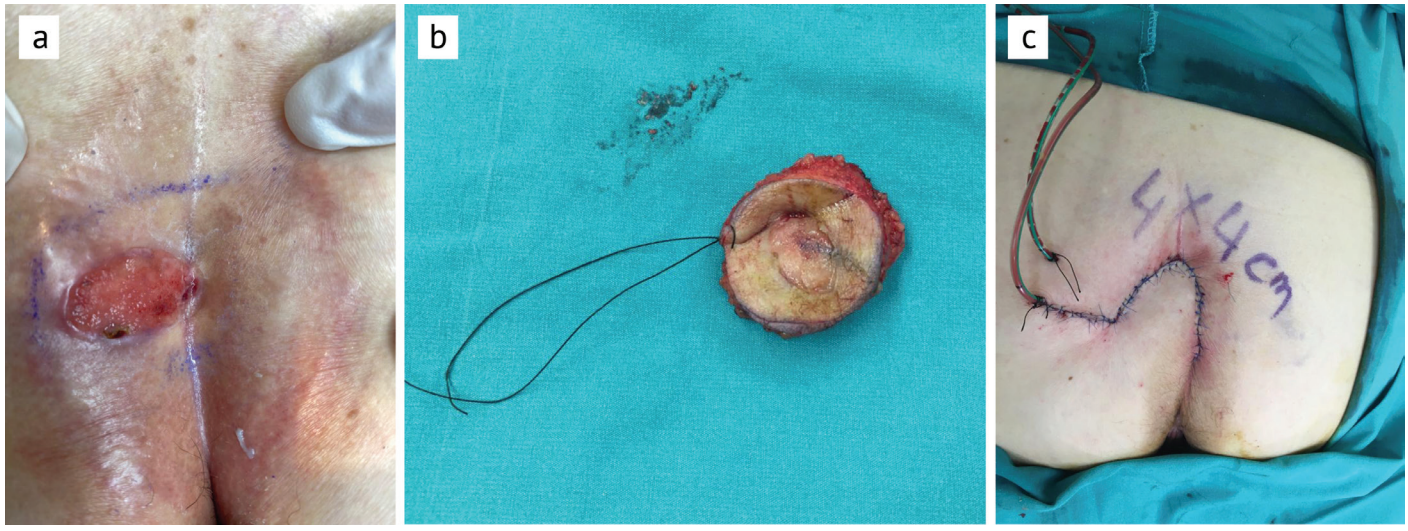


**Figure 3.** a) An ulcerated lesion at the intergluteal sulcus. b) Surgical specimen. c) Defect closure with Limberg flap

### Ethics

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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**Conflict of Interest:** No conflict of interest was declared by the authors.

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