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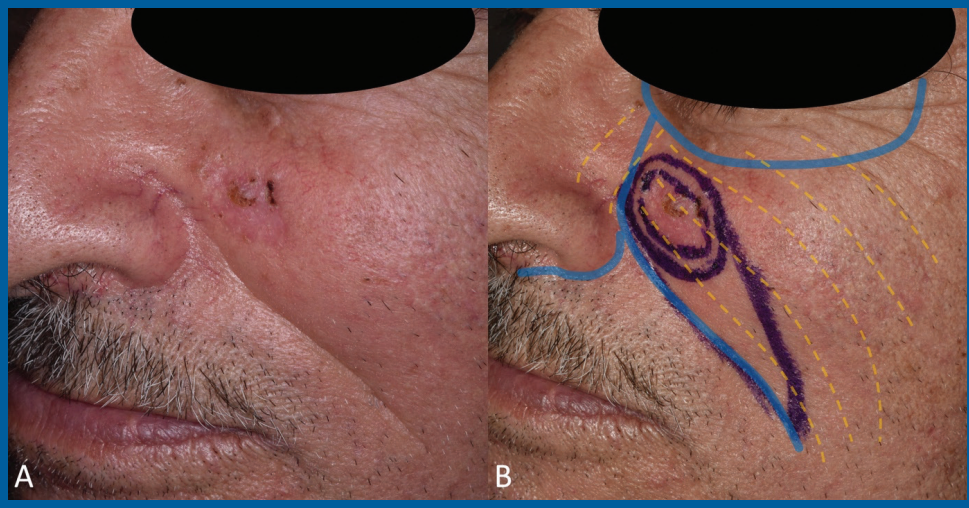


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Orginal Article

# Tumours of Skin and Adnexa: A Histopathological Cross-Sectional Study

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## Abstract

**Aim:** Pathologists and dermatologists face a major challenge in the diagnosis and treatment of skin and adnexal tumors due to limited clinical and pathological data. Adnexal tumors in old age tend to mimic malignant tumors. Histopathological examination is the mainstay for differentiating between benign and malignant tumors of the skin and adnexa because of the limited use of immunohistochemistry. Primary objective: To study the histopathological features of skin and adnexal tumors. Secondary - to classify various skin and adnexal tumors according to the World Health Organization classification and to study variations according to age, sex and site. A descriptive, cross-sectional study with statistical analysis.

**Materials and Methods:** This study was conducted in the pathology department of a tertiary care hospital in Central India. Total 190 samples were submitted. Collected data were analyzed by performing chi-square test using SPSS V.16 software.

**Results:** Out of 190 cases, 127 cases were diagnosed as benign and 63 cases were malignant tumors of the skin and adnexa; 42.1% cases were of keratinocytic origin. Malignant keratinocytic tumors were the most common. The study included 101 females and 89 males. The majority of cases (49%) occurred in the head and neck region. Neurofibroma is the most common benign skin tumor.

**Conclusion:** Skin tumors and their various histological types always create diagnostic difficulties. Histopathology is the gold standard that aids in the early diagnosis of skin and adnexal tumors, thus improving the prognosis.

**Keywords:** Skin, adnexa, tumours, histopathology

## Introduction

A wide variety of benign and malignant skin tumors occur in clinical setting mentioned as "troubling tumors" by Cotton[1,2] Their frequency varies due to different skin types, geographic location, occupational and sun exposure, skin protection awareness and its surveillance.[3] Their frequency increases with age.[4] In India, skin tumors constitute 1-2% of all cancers.[5] They were classified into three categories involving the epidermis, dermis, and adnexa, respectively.[6] Undifferentiated pluripotent stem cells, genetic influence, local vascularity, and the the microenvironment of the epidermis and dermis give rise to these tumors.[7] Because the use of immunohistochemistry is limited, histopathological examination is essential for correct diagnosis and management.

## Materials and Methods

This study was a cross-sectional study conducted in the pathology department of a tertiary care center in Central India for two years. A total of 190 samples were submitted, which included skin, wedge, edge, and excisional biopsies. The patient's clinical history was noted. Samples were processed routinely with hematoxylin and eosin staining. Special stains such as Periodic acid-Schiff, Masson's Trichrome, and Masson-Fontana were used when required. Approval from the institutional ethics committee and informed consent from patients were obtained. Histopathologically confirmed diagnoses of skin and adnexal tumors were included.

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### Statistical analysis

Statistical analysis was performed using SPSS V.16 software. $P < 0.05$ was considered statistically significant.

## Results

In the present study, 190 cases of skin tumors were included, of which 127 and 63 cases were benign and malignant tumors, respectively. The benign to malignant tumor ratio is 2.03:1. Cases were classified according to the World Health Organization (WHO) classification of skin tumors (Table 1), showing that 80 (42.1%) cases were of keratinocytic origin followed by appendageal origin (30 cases, 15.8%). Malignant keratinocytic tumors were the most common, accounting for 53 (27.9%) cases, followed by 27 (14.2%) cases of benign keratinocytic and neural tumors. Out of 190 cases, 101 and 89 cases were females and males, respectively, with male to female ratio: 1:1.13. Head and neck region (n = 94, 49%) was most common site followed by extremities (n = 42, 22.6%), trunk (n = 41, 22.5%) and external genitalia (n = 13, 6.8%). Most commonly benign tumours were noted in 3$^{th}$ decade (34 cases) and 4$^{th}$ decade (21 cases) and malignant tumours were in 6$^{th}$ and 7$^{th}$ decades accounting 14 and 16 cases, respectively.

In the present study, keratinocytic tumors comprised 27 (33.75%) benign and 53 (66.25%) malignant cases. Seborrheic keratosis was the most common benign tumor, followed by verruca vulgaris. Malignant keratinocytic tumors comprise 32 (60.4%) cases of squamous cell carcinoma and 21 (39.6%) cases of basal cell carcinoma (Table 2). Of 32 cases of SCC, 21 cases were observed in males and 11 cases in females. External genitalia were the most common site of occurrence, accounting for 40.6% of cases, followed by the lower extremities. Most cases of SCC were noted in the 5$^{th}$ to 7$^{th}$ decade. Out of 21 cases of BCC, 13 cases were seen in males. 90% cases were seen in the head and neck, and the eyelid was the most common site. In the present study, melanocytic tumors comprised 18 benign and 6 malignant cases. Intradermal nevus and malignant melanoma were the most common benign and malignant melanocytic tumors, respectively (Table 3). Malignant melanoma showed equal distribution in males and females. Foot was the most common site. In the present study, appendageal tumors comprised 26 benign and 4 malignant cases. The majority of cases belong to sweat gland differentiation. Cylindroma and hidradenoma were the most common tumors encountered (Table 4). Benign appendageal tumor shows female predominance with male-to-female ratio of 1:1.3. Malignant appendageal tumors comprise 2 cases each trichilemmal carcinoma and sebaceous carcinoma with female predominance. The most common site was the head and neck region in both. In the present study, 27 (14.21%), 24 (12.6%) and 5 (2.6%) cases were of neural, vascular and smooth muscle origin, respectively. All were benign tumors. The most common neural tumor was neurofibroma (n = 23) followed by schwannoma. Vascular tumors comprising 14 cases of lobular capillary hemangioma followed by 03 cases each of lymphangioma and angiokeratoma, 02 cases each of cherry angioma and epitheloid hemangioma. Piloleiomyoma (n = 4) was the most common smooth muscle tumor followed by a single case of angioleiomyoma.

**Table 1. Classification of skin tumors according to World Health Organization-2018**

| Tumours | Benign | Malignant | Total |
|---|---|---|---|
| Keratinocytic/epidermal | 27 (21.25%) | 53 (84.12%) | **80 (42.1%)** |
| Appendageal | 26 (20.47%) | 4 (6.3%) | **30 (15.8%)** |
| Neural | 27 (21.25%) | 00 | **27 (14.2%)** |
| Vascular | 24 (18.89%) | 00 | **24 (12.6%)** |
| Smooth muscle | 5 (3.93%) | 00 | **5 (2.7%)** |
| Melanocytic | 18 (14.17%) | 6 (9.52%) | **24 (12.6%)** |
| **Total** | **127 (66.84%)** | **63 (33.15%)** | **190 (100%)** |

$\chi^2$=58.9, $P < 0.001$ (highly significant)

**Table 2. Spectrum and frequency of keratinocytic tumors**

| Keratinocytic tumours | | | | | |
|---|---|---|---|---|---|
| **Benign tumours** | **No of cases** | **%** | **Malignant tumours** | **No of cases** | **%** |
| Actinic keratosis | 02 | 1.5 | Basal cell carcinoma | 21 | 33.3 |
| Seborrhoiec keratosis | 12 | 9.4 | Squamous cell carcinoma | 32 | 50.7 |
| Verruca plana | 01 | 0.7 | | | |
| Verruca vulgaris | 11 | 8.6 | | | |
| Warty dyskeratoma | 01 | 0.7 | | | |
| **Total** | **27** | **21.2** | | **53** | **84.1** |

**Table 3. Spectrum and frequency of melanocytic tumors**

| Melanocytic tumours | | | | | |
|---|---|---|---|---|---|
| **Benign tumours** | **No of cases** | **%** | **Malignant tumours** | **No of cases** | **%** |
| Blue nevus | 02 | 1.5 | Malignant melanoma | 06 | 9.5 |
| Compound nevus | 01 | 0.7 | | | |
| Congenital melanocytic nevus | 01 | 0.7 | | | |
| Dermal nevus | 02 | 1.5 | | | |
| Halo nevus | 01 | 0.7 | | | |
| Intradermal nevus | 10 | 7.8 | | | |
| Lentigenous compound nevus | 01 | 0.7 | | | |
| **Total** | **18** | **14.1** | | **06** | **9.5** |

**Table 4. Spectrum and frequency of appendageal tumors**

| Appendageal tumours | | | | | |
|---|---|---|---|---|---|
| **Benign tumours** | **No of cases** | **%** | **Malignant tumours** | **No of cases** | **%** |
| **Hair follicle differentiation** | **7** | **5.5** | | **02** | **3.1** |
| Pilomatricoma | 03 | 2.3 | Trichilemmal carcinoma | 02 | 3.1 |
| Trichofolliculoma | 01 | 0.7 | | | |
| Trichoadenoma | 01 | 0.7 | | | |
| Trichoepithelioma | 02 | 1.5 | | | |
| **Sweat gland differentiation** | **18** | **14.1** | | | |
| Chondroid syringoma | 02 | 1.5 | | | |
| Cylindroma | 04 | 3.1 | | | |
| Eccrine poroma | 03 | 2.3 | | | |
| Hidradenoma | 03 | 2.3 | | | |
| Hidroadenoma | 04 | 3.1 | | | |
| Syringoma | 02 | 1.5 | | | |
| **Sebaceous gland differentiation** | **01** | **0.7** | | **02** | **3.1** |
| Sebaceoma | 01 | 0.7 | Sebaceous carcinoma | 02 | 3.1 |
| **Total** | **26** | **20.4** | | **04** | **6.3** |

## Discussion

This study was conducted to assess the age, sex, and site-wise distribution of various skin and appendageal tumors and classified them according to the WHO classification. A total of 190 cases were studied, out of which 127 (67%) were benign and 63 (33%) were malignant, which is consistent with the study by Har-Shai et al.[8] and Vaibhav et al.[5] who noted 68.4% cases of benign and 31.6% cases of malignant tumors and 51.2% cases were malignant and 48.8% of cases were benign tumors, respectively. Out of 190 cases, 80 (42.1%) cases were of keratinocytic origin, 30 (15.8%) cases were of appendageal origin, 27 (14.2%) cases were of neural origin, 24 (12.6%) cases each of melanocytic and vascular origin, and 5 (2.7%) cases were of smooth muscle origin. Keratinocytic tumors were the most common tumors. These findings were comparable with the study by Vaibhav et al.,[5] Kale and Bagate[9], Sherpa and Raj KC.[10] We noted 101 (53.1%) and 89 (46.9%) cases were in females and males, respectively, which was comparable with the findings by Pappala et al.[11] In present study, the most common presentation was in the head and neck region (49.47%) followed by extremities (22.1%), trunk (21.57%), and external genitalia (6.84%), which were comparable with the study by Shrivastav et al.[12] and Uplaonkar et al.[13] Skin tumors were presented in a wide age range varies from 1$^{st}$ decade to 9$^{th}$ decade in the present study. The majority of benign tumors were presented in the 3$^{th}$ and 4$^{th}$ decade, and the majority of malignant tumors were presented in the 6$^{th}$ and 7$^{th}$ decade. Similar observations noted by Gundalli et al.[14] where 52.83% cases of benign tumors belonged to 3$^{rd}$ to 5$^{th}$ decade and 78.75% cases of malignant tumors belonged to 6$^{th}$ to 8$^{th}$ decade. Goel et al.[15] observed that majority of benign tumors were in 3$^{rd}$ decade (26.9%) and 26.6% cases of malignant tumors were in 7$^{th}$ decade. In present study, majority of benign tumors were of keratinocytic origin (n = 27, 21.2%) and neural origin (n = 27, 21.2%) followed by appendageal tumors (n = 26, 20.4%), vascular tumors (n = 24, 18.8%), melanocytic tumors (n = 18, 14.1%) and smooth muscle origin

tumors (n = 5, 3.9%), which were comparable with the study done by Kale and Bagate[9] and Sherpa and Raj KC.[10] The majority of malignant tumors were of keratinocytic origin (84%) followed by melanocytic origin (9.5%) and appendageal origin (6%). Squamous cell carcinoma accounted for the majority of the cases (50.7%), which was also observed by Chakravorty and Dutta-Choudhuri,[16] Budhraja et al.,[17] Deo et al.,[18] and Laishram et al.[19] We noted that seborrheic keratosis was the most common benign keratinocytic tumor followed by verruca vulgaris. Goel et al.[15] observed a majority of cases of verruca vulgaris followed by seborrheic keratosis. Polat et al.[20] observed a majority of cases of actinic keratosis followed by seborrheic keratosis. These variations in distribution could be due to geographical variation. We noted 12 cases of seborrheic keratosis with a male-to-female ratio of 1.4:1. Maximum cases were presented in 6$^{th}$ and 7$^{th}$ decades. Seven cases were located in the head and neck followed by the trunk region. Histology revealed acanthosis hyperkeratosis, papillomatosis, and parakeratosis with proliferation of basaloid cells and squamous cells and a keratin-filled horn cyst. Similar findings were observed by Bandyopadhyay et al.[21] 11 cases of verruca vulgaris were encountered with female predominance, and the most common site was the head and neck and were presented between 21 to 70 years. Histology revealed acanthosis, hyperkeratosis, parakeratosis, and papillomatosis. Kilkenny et al.[22] also found similar findings. Two cases of actinic keratosis were encountered; both were noted in males and on the back. Similar observations were studied by Roewert-Huber et al.[23] Histology revealed basaloid cells arranged in nodules with peripheral palisading and increased melanin pigmentation. A single case of verruca plana was encountered in a 16-year- old female over the trunk. Histology revealed hyperkeratosis and acanthosis with koilocytic changes in keratinocytes, which were consistent with observations by Pavithra et al.[24] Single case of warty dyskeratoma was noted in a 44-year-old female over the face. Histology showed suprabasilar clefting, acantholysis, dyskeratosis, and dysplastic changes, which were consistent with the findings of Harrist et al.[25] We noted that squamous cell carcinoma was the most common malignant keratinocytic tumor, accounting for 32 cases (50.7%), which was in accordance with the study by Budhraja et al.,[17] Chakravorty and Dutta-Choudhuri,[16] Deo et al.,[18] and Laishram et al.,[19] having an occurrence rate of 49.02%, 64.3%, 55.8%, 43.6% respectively. The majority of cases were males (21/32), compared to females (11/32), with the male to female ratio being 1.9:1. The most common site of SCC was the external genitalia, followed by the extremities, head and neck region, and trunk. Similar observations were noted by Budhraja et al.,[17] Deo et al.,[18] and Laishram et al.[19] Majority of SCC cases were presented in 5$^{th}$ to 7$^{th}$ decade which was similar to the study by Kaur et al.[26] and Vaibhav et al.[5] Histology of maximum cases showed sheets and nests of malignant squamous cells that invaded deeper tissue. Cells having hyperchromatic, pleomorphic nuclei with moderate amounts of cytoplasm and keratin pearl formation (Figure 1). These findings were similar to those reported by Rupashree and Geethalakshmi[27] and Chakravorty and Dutta-Choudhuri.[16] We noted 21 cases of basal cell carcinoma, of which 13 cases were in males and 8 cases were females. Maximum cases were seen in the head and neck region. The mean age of presentation was 61 years, and peak incidence was seen in 7$^{th}$ decade where the youngest case was seen in a 31-year-old female and the eldest one in a 92-year-old female. These were consistent with the findings by Solanki et al.[28], Chakravorty and Dutta-Choudhuri[16], and Budhraja et al.[17] Keratotic BCC was the most common type noted, whereas in Solanki et al.,[28] solid BCC was the most common type. Baruah et al.[29] and Adinarayan and Krisshnamurthy[30] reported the nodular variant as the most common type. On histology, the majority of cases showed nests of basaloid cells with peripheral palisading and clefting artifacts (Figure 2). Marked melanosis was observed in three cases of pigmented BCC. One case of basosquamous BCC showed atypical squamous cells. We observed 24 cases of melanocytic tumors, including 18 benign and 6 malignant cases. Intradermal nevus (n = 10) was the most common benign tumor, followed by blue nevus (n = 2) and dermal nevus (n = 2). We observed 10 cases of intradermal nevus, of which 6 were seen in females. The majority of cases were located in the head and neck region followed by the trunk. Age of presentation varies between 1 and 50 years, with the youngest being an 8-year-old male over the trunk region. Histology revealed hyperkeratosis with increased basal cell pigmentation and dermis showing sheets and nest of nevus cells with intracytoplasmic melanin pigment. Two cases of blue nevus were encountered, both in females over the head and neck region. Histology showed proliferation of round,

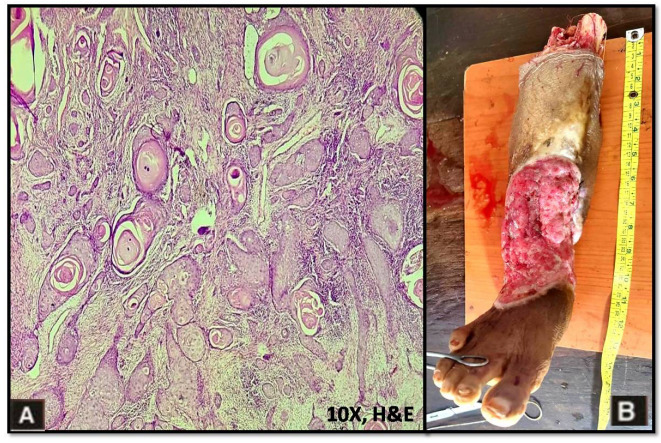


**Figure 1.** (A) Photomicrograph (x10; hematoxylin and eosin) of squamous cell carcinoma showing islands, nests, and sheets of malignant squamous cells with keratin pearls. (B) Gross: Photograph of the below-knee amputated specimen of SCC showing ulcerated growth

oval to spindle cells with melanin pigmentation, which was consistent with the findings of Rubinstein et al.[31]. We observed 2 cases of dermal nevus both in females, which occurred in the head and neck region. Histology revealed nevus cells with melanin pigment extending into the lower dermis and adnexal structures. A single case of compound nevus was seen in a 44-year-old male over the head and neck region. Histology showed nest of nevus cells throughout the dermis. A single case of halo nevus noted in a 13-year-old male over the upper extremity. Histology revealed a nest of nevus cells along with dense lymphocytic infiltrates in the dermis. Our observations were comparable with the findings observed in a study conducted by Shoko[32] and Mooney et al.[33] We observed six cases of malignant melanoma showing equal incidence in males and females; however, in the study conducted by Sampat and Sirsat[34], Mukhopadhyay et al.,[35] and Katalinic et al.,[36] male predominance was observed. Maximum cases were seen in the extremities, which was in accordance with the study done by Sampat and Sirsat[34] and Mukhopadhyay et al.[35] The majority (83.3%) cases were seen on the foot region. Similar observations were noted by Sampat and Sirsat[34], Budhraja et al.[17] and Ochicha et al.[37] in 54%, 83%, and 93% cases, respectively. Histology revealed nests and groups of polygonal cells having pleomorphic hyperchromatic nuclei with moderate amounts of cytoplasm, and intracellular melanin pigment deposition was also noted (Figure 3). In present study, 30 (15.8%) cases of appendageal tumors were noted, of which 26 and 4 cases were benign and malignant, respectively, which was consistent with the findings observed by Reddy et al.[38] and Vaishnav and Dharkar.[39] Appendageal tumors were differentiated into sweat gland tumors (69.2%), hair follicle tumors (27%) and sebaceous gland tumors (3.8%), consistent with the findings of Nair[40] and Solanki et al.[41] We observed 7 cases of benign hair follicular tumors, of which 5 were seen in females and 2 in males, which were consistent with the study done by Marrogi et al.[42] Pilomatricoma and trichoepithelioma were the most common. Similar observations were made by Kartha et al.[43], and Solanki et al.[41] Three cases of pilomatricoma were noted with female predominance and were presented between 11 and 40 years of age, commonly located in the head and neck. Histology revealed proliferation of basal cells, shadow cells, calcification, and keratinization, which were consistent with observations made by Solanki et al.[41] Two cases of trichopeithelioma were found with equal sex incidence and located in the head and neck region. Histology revealed islands of basaloid cells with peripheral palisading and multiple keratinous horn cysts with papillary mesenchymal bodies (Figure 4). Similar findings were noted by Dissanayaka et al.[44] We observed 18 benign cases of sweat gland tumors. Hidradenoma and cylindroma were the most common. Four cases of cylindroma were noted, all were seen in females and located in the head and neck. The youngest case was presented

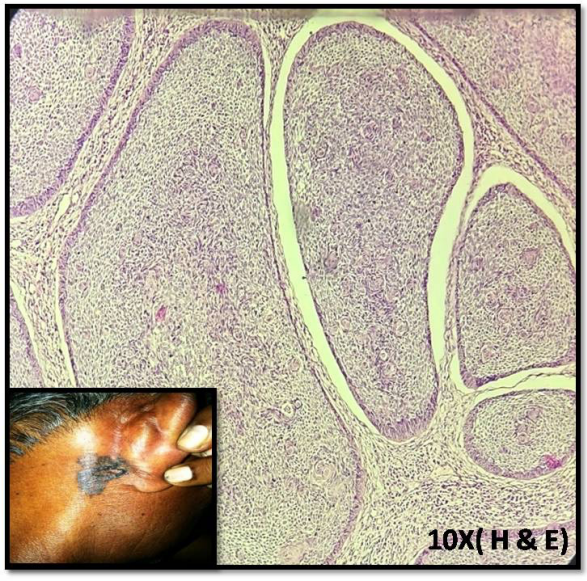


**Figure 2.** Photomicrograph (x10; hematoxylin and eosin) of basal cell carcinoma showing tumor arranged in islands of basaloid cells with peripheral palisading and clefting artefact inset - 3x2 cm blackish-colored skin lesion in the post- auricular region

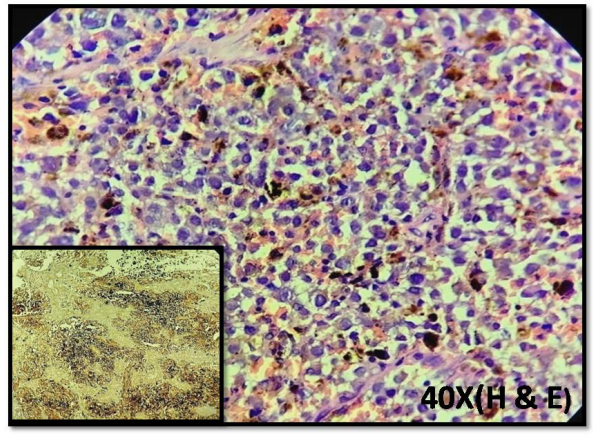


**Figure 3.** Photomicrograph (x40; hematoxylin and eosin) of malignant melanoma showing nests and groups of tumor cells with intracellular melanin pigment deposition. Inset - Masson-Fontana stain (x10) showing brown melanin pigment


**Figure 4.** (A) Photograph showing multiple skin-colored papules over the nose, forehead, and periorbital region. (B) Photomicrograph (x10, hematoxylin and eosin) of trichoepithelioma showing islands of basaloid cells with peripheral palisading and multiple keratinous horn cysts

in a 17-year-old female and the eldest was in a 76-year-old female. Histology revealed islands of basaloid cells with peripheral palisading separated by an acellular eosinophilic hyaline sheath and basaloid cells arranged in a jigsaw puzzle pattern (Figure 5). Similar observations were noted by Berke and Grant-Kels[45] four cases of hidradenoma were encountered with male predominance and commonly presented in 51-60 years with head and neck involvement. Similar observations were noted by Solanki et al.[41] Histology revealed polygonal to cuboidal cells arranged in a lobular pattern with round to elongated nuclei with granular cytoplasm and few lumina lined by columnar to cuboidal cells. Two cases of chondroid syringoma were encountered with a male to female ratio 1:1. Histology showed a biphasic cell population with epithelial cells in the cord and nests and a nest of squamous cells with horn cysts and keratin formation. The stromal component showed a myxoid, chondroid, and hyaline matrix. Similar observations were noted by Berke and Grant-Kels[45] three cases of eccrine poroma were noted, presented in 41-80 years of age and located over the head and neck, lower extremities, and trunk. Histology revealed anastomosing bands of epithelial cells in the dermis and cuboidal cells with round nuclei and moderate cytoplasm. Similar findings were noted by Wankhade et al.[46] We noted a single case of sebaceoma in a 21-year-old male over the scalp. Histology revealed nests of basaloid cells and sebaceous cells. Similar observations were noted by Ahmed et al.[47], and David[48]; we encountered four cases (6.3%) of malignant appendageal tumors comprising 2 cases each of hair follicle and sebaceous gland differentiation. We noted 2 cases of trichilemmal carcinoma, both located in the head and neck and in females. Histology revealed islands of basaloid cells with peripheral palisading and trichilemmal-type keratinization at certain sites (Figure 6). These findings were consistent with those of the study by Lee et al.[49] We noted 2 cases of sebaceous carcinoma, both in females and located on the head and neck, which were consistent with the observations by Wali and Al-Mujaini.[50] Histology revealed lobules of pleomorphic sebaceous cells separated by fibrovascular stroma, polygonal cells with eosinophilic cytoplasm, pleomorphic nuclei with coarse chromatin, and prominent nucleoli. In the present study, 27 benign cases of neural tumors were noted, of which neurofibroma was the most common. Twenty-three cases of neurofibroma were encountered with female predominance and majority located in the head and neck followed by the trunk. The youngest case was seen in a 7-year-old male over the head and neck. Histology revealed a well-circumscribed mass with fascicular and palisading arrangement of spindle cells with a wavy elongated nucleus. Similar observations were noted by Ortonne et al.[51] In the present study, 24 cases of benign vascular tumors were encountered, and lobular capillary haemgioma was the most common tumour. Fourteen cases of lobular capillary hemangioma were noted with female predominance and located in the head and neck followed by the trunk and upper extremities, commonly presented in 21-70

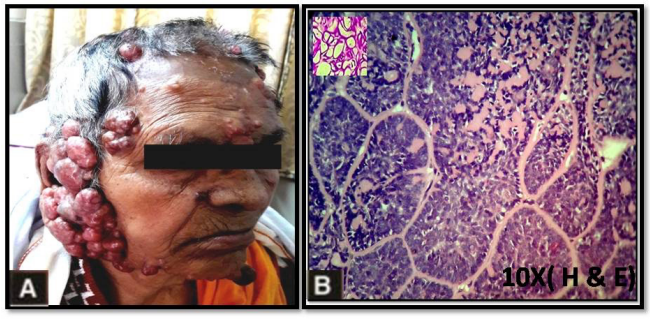


**Figure 5.** (A) Photograph showing multiple skin colored to erythematous nodules of varying size over the head and neck region. (B) Photomicrograph (x10, hematoxylin and eosin) of cylindroma showing islands of basaloid cells separated by a hyaline sheath in a jigsaw puzzle-like arrangement with hyaline droplets. Inset - PAS stain positivity of hyaline material

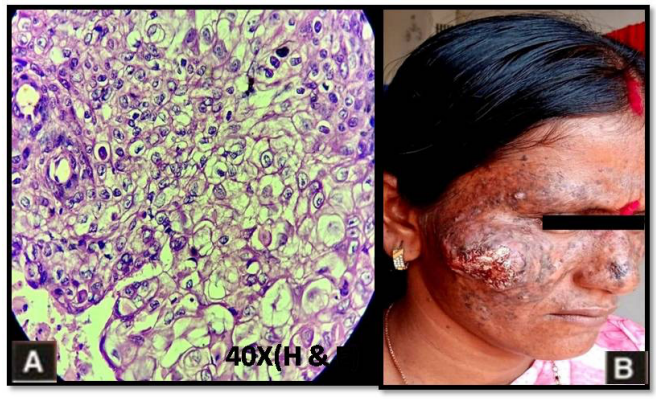


**Figure 6.** (A) Photomicrograph (x40; hematoxylin and eosin) of trichilemmal carcinoma showing tumorarranged in nest, lobules of clear cells with vacuolated cytoplasm, pleomorphic hyperchromatic nuclei, nuclear palisading, and mitosis with pilar- type keratinization. (B) Photograph showing ulcerative growth over face with rolled out margin

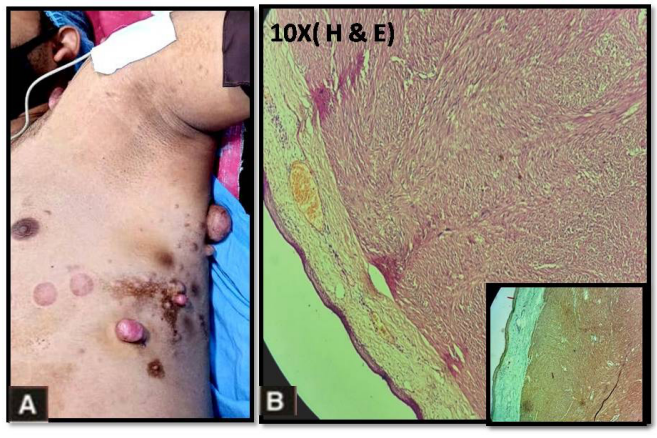


**Figure 7.** (A) Photograph showing multiple nodules over the abdomen and back. (B) Photomicrograph (x10, hematoxylin and eosin) of piloleiomyoma showing spindle cells arranged in bundles, fascicles, and whorls. Inset - Masson Trichrome stain (x10) showing red-colored smooth muscle fibers

years. Histology revealed lobules of variable-sized capillaries lined by plump endothelial cells. Similar findings were observed by Mills et al.[52] We observed 5 cases of benign smooth muscle tumors, of which 4 cases were of piloleiomyoma with equal gender occurrence and commonly located at the trunk followed by the head and neck. Histology revealed a well-circumscribed mass comprising spindle cells arranged in bundles, fascicles, and whorls (Figure 7). Similar observations were noted by Albuquerque et al.[53]

## Conclusion

Skin is a complex and largest organ of the body with various lesions, including tumors from the epidermis, its appendages, and dermis. The varied presentation of skin tumors poses a diagnostic challenge to clinicians, and their distinctions into benign and malignant neoplasms are more difficult. Skin appendageal tumors are difficult to diagnose by clinicians and pathologists because of their similar clinical presentation and wide histomorphological differentiation along different lines in the same lesion. Histological study of skin tumors emphasizes the various patterns of skin tumors in a particular geographical location. Histopathological examination is the gold standard for the definite diagnosis of various skin tumors, which helps clinicians to improve the therapeutic approach and emphasize the importance of early diagnosis of malignant tumors owing to its prognostic implication and effective management.

### Ethics

**Ethics Committee Approval:** Approval from the institutional ethics committee were obtained.

**Informed Consent:** Informed consent from patients were obtained.

### Authorship Contributions

Concept: V.P.M., S.B.H., S.M.C., E.A.R., Design: V.P.M., S.B.H., S.M.C., E.A.R., Data Collection or Processing: V.P.M., S.B.H., S.M.C., E.A.R., Analysis or Interpretation: V.P.M., S.B.H., S.M.C., E.A.R., Literature Search: V.P.M., S.B.H., S.M.C., E.A.R., Writing: V.P.M., S.B.H., S.M.C., E.A.R.

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Orginal Article

# Effect of the COVID-19 Pandemic on the Academic Publishing Behavior of Dermatologists

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## Abstract

**Aim:** The coronavirus disease-2019 (COVID-19) pandemic since its inception, has significantly impacted the academic activities of medical doctors. The decrease in physicians' workload and the urge to share new knowledge about the new disorder caused medical doctors to write and publish academic papers rapidly. We investigated the effects of the pandemic on the academic publishing behavior of dermatologists in Turkey.

**Materials and Methods:** The study was conducted through a PubMed search using the keywords "Dermatology Turkey". Search limits were set for 2017-2019 for the pre-pandemic period and 2020-2022 for the post-pandemic era. Irrelevant articles were manually excluded. The publication year, type and subject of publication, whether the study was multicenter or multidisciplinary, and the journal were noted for each paper. Data obtained were analyzed using the IBM SPSS Statistics 25 package program.

**Results:** The search revealed 986 and 1420 articles for the pre- and post-pandemic periods, respectively. The most published subjects were drugs and drug eruptions before the pandemic and COVID-19 after the pandemic. An increase in the ratio of "letters to editors" and in multicenter studies was noted in the post-pandemic era. The distribution among the journals of publication changed strikingly, and 35.8% of papers were published in only two journals after the pandemic.

**Conclusion:** There were significant changes in the publishing behavior of Turkish dermatologists during the pandemic. We believe that this study is important as a demonstration of the academic behaviors of dermatologists and a guide for young dermatologists who wish to publish.

**Keywords:** Academic publishing, COVID-19, dermatology

## Introduction

The coronavirus disease-2019 (COVID-19) pandemic, which started at the end of the year 2019, led to many changes in all areas of life, including the academic activities of medical doctors. The restrictions on the number of patients seen at outpatient clinics at the beginning of the pandemic caused a decrease in the clinical workload of physicians. Additionally, academic physicians were eager to share the findings and data they obtained about the new disease, and many scientific journals and publishers promoted articles about COVID-19 by offering fast-track and open-access publishing for these papers.[1] This led to a substantial change in the academic productivity of physicians worldwide and more published articles.

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In this study, we aimed to investigate the effects of the COVID-19 pandemic on the academic behavior of Turkish dermatologists, namely the changes in the number and types of scientific papers and their contents.

## Materials and Methods

Scientific dermatology publications from Turkey were evaluated in two groups: pre-pandemic for the last three years before the onset of the COVID-19 pandemic and post-pandemic for the period after the pandemic started. Only articles published in PubMed were included in this

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study. A PubMed search was conducted for the keywords "Dermatology Turkey" on August 5, 2022. Search restrictions were set for papers published between 2017 and 2019 for the pre-pandemic period and 2020-2022 for the post-pandemic period. The papers from 2022 were included until August. The listed articles were manually selected to include at least one dermatologist from Turkey. The dataset was constructed to include the year of publication, a type of publication, subject, status of being multicenter and multidisciplinary, and journal name. The impact factors of the journals were noted. For statistical analysis, the journals that published less than ten dermatology publications from Turkey were grouped under the title "other". Papers published before 2017 and after the 5th August 2022, lacking a dermatologist from Turkey among authors and not indexed in PubMed, were excluded from the study. The subject groups are depicted in Table 1.

### Statistical analysis

Data were analyzed using the IBM SPSS Statistics 25 package program. Descriptive statistics were given in terms of frequency and percentage, whereas comparative statistics between pre- and post-pandemic publications were conducted using the chi-square test. Confidence level was determined as 95%, and *P* values 0.05 were accepted as statistically significant.

## Results

The PubMed search resulted in 1265 papers for the pre-pandemic and 1627 papers for the post-pandemic era. After manually excluding articles that did not meet the inclusion criteria, the pre- and post-pandemic groups included 986 and 1420 articles, respectively. An increase in the number of publications after the pandemic started was noticed (Figure 1).

The dermatology subjects with the highest numbers of publications were drugs and drug reactions (10.4%), psoriasis (9.3%), and connective tissue disorders/vasculitides (7.9%) in the pre-pandemic period. During the pandemic period, the most frequent subjects were COVID-19 (13.94%), psoriasis (8.59%), drugs and drug reactions (7%), and connective tissue disorders/vasculitides coming in the 4th place (5.7%) (Table 1). The most frequently published subjects significantly differed between the pre- and post-pandemic groups ($P = 0.001$).

Clinical study was the most frequent type of study published in both the pre- and post-pandemic periods (51.12% and 48.59%, respectively), followed by case reports in the pre-pandemic period (32.76%) and letters to editors in the post-pandemic period (32.76%) (Figure 2). The publication types differed significantly between the pre- and post-pandemic periods ($P < 0.001$).

Most of the studies published in both pre- and post-pandemic periods were conducted in a single center (64% and 56.6%, respectively). National and international multicenter study frequencies significantly increased during the pandemic ($P = 0.001$) (Figure 3). While most published studies were multidisciplinary during both periods, the frequency of multidisciplinary studies significantly decreased in the post-pandemic era ($P = 0.003$) (Figure 4).

Two hundred sixty-two journals published papers from the dermatology departments in Turkey before the pandemic. This number was 293 for the post-pandemic era. For the pre-pandemic period, the three journals with the highest number of publications from Turkish dermatologists were Dermatologic Therapy, Cutaneous and Ocular Toxicology, and Postepy Dermatologii I Alergologii. After the pandemic started, the highest number of papers were published in Dermatologic Therapy, Journal of Cosmetic Dermatology, and International Journal of Dermatology (Table 2). The distribution of journals was significantly different between the pre- and post-pandemic groups ($P < 0.001$). The distribution of the article subjects of the most popular journal (Dermatologic Therapy) (Table 3) was compared with that of the Indian Journal of Dermatology, Venereology and Leprology, a journal in which the percentage of articles from Turkish dermatologists had decreased in the post-pandemic era. While 28.21% of reports from Turkey published in Dermatologic Therapy were on COVID-19, there were no papers on COVID-19 in the Indian Journal of Dermatology, Venereology and Leprology, and a statistically significant difference was found ($P = 0.003$).

## Discussion

In this study, we evaluated the change in publication patterns of Turkish dermatologists throughout the COVID-19 pandemic. There has been a striking increase in the number of papers published by Turkish dermatologists at the beginning of the pandemic. This increase is arguably caused by the changes in the working conditions of physicians. In April 2020, the number of patients seen daily in outpatient clinics was dramatically decreased by the Ministry of Health to decrease circulation in hospitals and dedicate health services to the care of patients with COVID-19. Inpatient clinics considered less "busy" and less "urgent", among which were dermatology clinics, were shut down and replaced by COVID-19 wards. Many physicians, including dermatologists, were appointed to the COVID-19 clinics, where the healthcare personnel worked in shifts of 24 h followed by 48 to 72 hours' off time to avoid contamination and exhaustion. There were also nationwide lockdowns, so people, including physicians, were at home without much social interaction. All these factors contributed to an ample amount of free time for Turkish physicians, who,

under normal conditions, work very hard and see an average of 70 patients per day. Additionally, COVID-19 was a new disease, and medical doctors around the world, including those from Turkey, started to conduct research about this disease and publish their findings promptly to elucidate the clinical characteristics and pathophysiology of COVID-19.

The cut-off date for the post-pandemic period was set as August 2022, since in April 2022, the pandemic conditions in Turkey were put to an end entirely, including the shutting down of COVID-19 clinics at hospitals and the end of the obligation to wear a mask in public places.[2] Thus, we included three more months after this date to allow time for already submitted articles to be published.

**Table 1. Frequencies of publications in different subjects in the pre- and post-pandemic groups**

| | Groups | | | | | | |
|---|---|---|---|---|---|---|---|
| | Pre-pandemic | | Post-pandemic | | Total | | |
| Subjects | Freq. | % | Freq. | % | Freq. | % | *P* value |
| Acne | 35 | 3.5 | 57 | 4.0 | 92 | 3.8 | |
| Autoimmune bullous disorders | 31 | 3.1 | 34 | 2.4 | 65 | 2.7 | |
| Bacterial diseases | 19 | 1.9 | 8 | 0.6 | 27 | 1.1 | |
| Connective tissue disorders/vasculitides | 78 | 7.9 | 81 | 5.7 | 159 | 6.6 | |
| Cosmetic dermatology | 34 | 3.4 | 67 | 4.7 | 101 | 4.2 | |
| COVID-19 | 0 | 0.0 | 198 | 13.9 | 198 | 8.2 | |
| Cutaneous lymphoma | 19 | 1.9 | 34 | 2.4 | 53 | 2.2 | |
| Dermatitis | 29 | 2.9 | 54 | 3.8 | 83 | 3.4 | |
| Dermatologic surgery | 15 | 1.5 | 33 | 2.3 | 48 | 2.0 | |
| Dermoscopy | 68 | 6.9 | 77 | 5.4 | 145 | 6.0 | |
| Drugs & drug reactions | 103 | 10.4 | 100 | 7.0 | 203 | 8.4 | |
| Fungal diseases | 10 | 1.0 | 15 | 1.1 | 25 | 1.0 | |
| Genodermatoses | 50 | 5.1 | 34 | 2.4 | 84 | 3.5 | |
| Hair disorders | 40 | 4.1 | 59 | 4.2 | 99 | 4.1 | |
| Hidradenitis suppurativa | 9 | 0.9 | 25 | 1.8 | 34 | 1.4 | |
| Hyperhidrosis-ecrine gland disorders | 3 | 0.3 | 3 | 0.2 | 6 | 0.2 | |
| Insect/spider bites and ectoparasites | 0 | 0.0 | 4 | 0.3 | 4 | 0.2 | |
| Lichenoid disorders | 16 | 1.6 | 10 | 0.7 | 26 | 1.1 | **0.000*** |
| Melanoma | 11 | 1.1 | 13 | 0.9 | 24 | 1.0 | |
| Nail disorders | 6 | 0.6 | 5 | 0.4 | 11 | 0.5 | |
| Nevi | 10 | 1.0 | 6 | 0.4 | 16 | 0.7 | |
| Non-melanoma skin cancer | 27 | 2.7 | 40 | 2.8 | 67 | 2.8 | |
| Other | 67 | 6.8 | 48 | 3.4 | 115 | 4.8 | |
| Other neoplastic diseases | 27 | 2.7 | 30 | 2.1 | 57 | 2.4 | |
| Other papulosquamous diseases | 8 | 0.8 | 4 | 0.3 | 12 | 0.5 | |
| Parasitic disorders | 13 | 1.3 | 38 | 2.7 | 51 | 2.1 | |
| Pediatric dermatology | 23 | 2.3 | 18 | 1.3 | 41 | 1.7 | |
| Photodermatology | 6 | 0.6 | 5 | 0.4 | 11 | 0.5 | |
| Pruritus | 7 | 0.7 | 5 | 0.4 | 12 | 0.5 | |
| Psoriasis | 92 | 9.3 | 122 | 8.6 | 214 | 8.9 | |
| Psychodermatology | 8 | 0.8 | 20 | 1.4 | 28 | 1.2 | |
| Rosacea | 21 | 2.1 | 36 | 2.5 | 57 | 2.4 | |
| Systemic diseases and dermatology | 28 | 2.8 | 17 | 1.2 | 45 | 1.9 | |
| Urticaria | 40 | 4.1 | 75 | 5.3 | 115 | 4.8 | |
| Viral diseases | 16 | 1.6 | 23 | 1.6 | 39 | 1.6 | |
| Vitiligo | 17 | 1.7 | 22 | 1.5 | 39 | 1.6 | |
| Total | | | | | 2406 | 100.0 | |

*$P < 0.05$, COVID-19: Coronavirus disease-2019

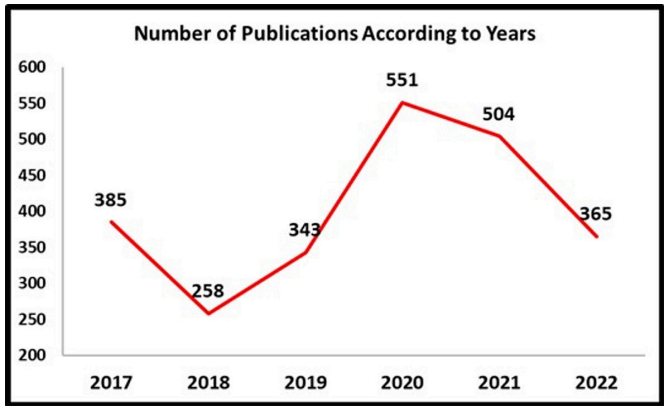


**Figure 1.** Number of publications performed by dermatologists from Turkey, according to year of publication. Note that the number from 2022 includes only the first seven months of the year

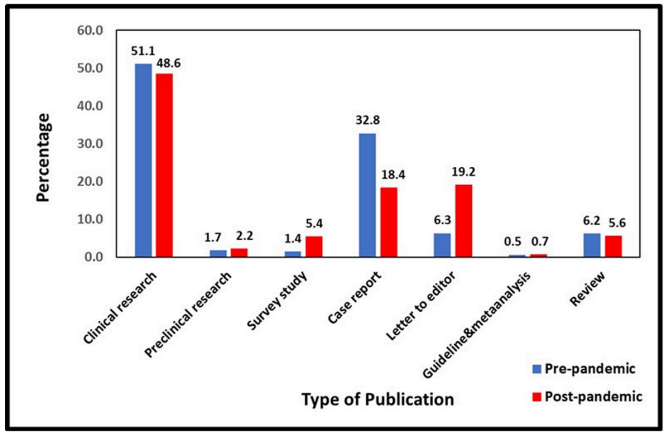


**Figure 2.** Distribution of types of publications in pre- (blue) and post-pandemic (red) periods

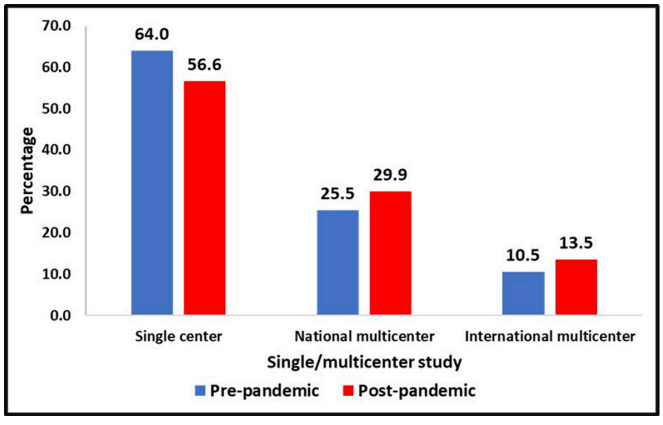


**Figure 3.** Frequencies of single- and multicenter studies published during the pre- or post-pandemic periods

As expected, the "hot topic" during the pandemic period was COVID-19; although it is not a primarily dermatologic disease, Turkish dermatologists seem to have published considerably on this subject, mainly about the cutaneous findings of COVID-19 and cutaneous drug reactions caused by COVID-19 treatment. Interestingly, the frequency of letters

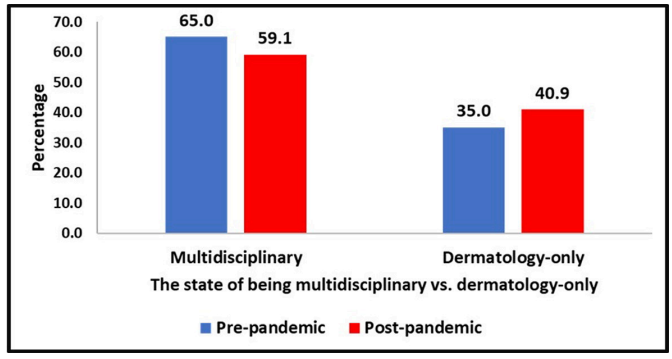


**Figure 4.** Frequencies of multidisciplinary and dermatology-only studies published during the pre- or post-pandemic periods

increased remarkably and replaced case reports as the second most common type of publication, following clinical research articles. This may partially be caused by the publishing policy of journals, i.e., removing case reports from their article types and accepting case presentations only in letter forms. The rapid publication process, which was especially important during the pandemic due to an increased amount of new data about the new disease, may be another reason for the authors to prefer letters over case reports.

Another remarkable finding is the low percentage of pre-clinical research among other article types by Turkish dermatologists. Although this percentage somewhat increased during the pandemic, it was still very low. Today, the general approach to advances in medicine involves "bench to bedside," and we believe that increased efforts in pre-clinical research in the field of dermatology would allow Turkish dermatologists to make better and more relevant contributions to the literature.

One of our most striking findings was that in the post-pandemic period, 35.8% of all articles from Turkish dermatologists were published in only two journals, Dermatologic Therapy and Journal of Cosmetic Dermatology. This is indeed an astonishing finding worth considering. We have a few opinions on why this trend occurred. First, academicians from Turkey have a hard time publishing in general, probably partly because of the quality of papers (due to language challenges since English is not our primary language, low economic sources to produce high-impact scientific research, and time limitations due to high patient numbers seen per clinic day, enforced by the government healthcare system policies). Some journals and editors may be biased or prejudiced against papers from Turkey. Therefore, a Turkish physician-researcher tends to look for journals that have previously published material from Turkey before submitting their work. Thus, a journal that has published articles from Turkey has a higher probability of receiving more and more submissions from Turkey. Second, many journals changed their publishing policies during the COVID-19 pandemic,

**Table 2. Distribution of journals in which papers from Turkish dermatologists were published. Journal impact factors were obtained from the Web of Science where applicable, and from Scimago Journal & Country Rank for journals not indexed in the Web of Science**

| Journal | Groups | | | | | | Total | | Impact factor | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-pandemic | | | Post-pandemic | | | | | | |
| | Freq. | % | Year** | Freq. | % | Year** | Freq. | % | | |
| Dermatol Ther | 59 | 6.0 | 2019 | 274 | 19.3 | 2021 | 333 | 13.8 | 3.6 | |
| J Cosmet Dermatol | 13 | 1.3 | 2018 | 234 | 16.5 | 2021 | 247 | 10.3 | 2.3 | |
| Int J Dermatol | 30 | 3.0 | 2018 | 44 | 3.1 | 2021 | 74 | 3.1 | 3.6 | |
| Postepy Dermatol Alergol | 37 | 3.8 | 2018 | 33 | 2.3 | 2020 | 70 | 2.9 | 1.4 | |
| J Eur Acad Dermatol Venereol | 29 | 2.9 | 2018 | 39 | 2.7 | 2021 | 68 | 2.8 | 9.2 | |
| Cutan Ocul Toxicol | 41 | 4.2 | 2018 | 23 | 1.6 | 2021 | 64 | 2.7 | 1.6 | |
| An Bras Dermatol | 28 | 2.8 | 2018 | 31 | 2.2 | 2021 | 59 | 2.5 | 1.7 | |
| Clin Exp Dermatol | 17 | 1.7 | 2018 | 31 | 2.2 | 2021 | 48 | 2.0 | 4.1 | |
| Indian J Dermatol | 27 | 2.7 | 2018 | 22 | 1.5 | 2021 | 49 | 2.0 | 1.7 | |
| Dermatol Pract Concept | 21 | 2.1 | 2018 | 25 | 1.8 | 2021 | 46 | 1.9 | 2.8 | |
| Australas J Dermatol | 21 | 2.1 | 2018 | 21 | 1.5 | 2021 | 42 | 1.7 | 2 | |
| Indian J Dermatol Venereol Leprol | 23 | 2.3 | 2018 | 14 | 1.0 | 2021 | 37 | 1.5 | 2.9 | |
| Clin Dermatol | 25 | 2.5 | 2018 | 11 | 0.8 | 2021 | 36 | 1.5 | 2.7 | |
| J Dermatolog Treat | 13 | 1.3 | 2018 | 21 | 1.5 | 2021 | 34 | 1.4 | 2.9 | |
| Int J Clin Pract | 0 | 0 | - | 33 | 2.3 | 2021 | 33 | 1.4 | 2.6 | |
| Turk J Med Sci | 15 | 1.5 | 2018 | 15 | 1.1 | 2020 | 30 | 1.2 | 2.3 | |
| Acta Dermatovenerol Alp Pannonica Adriat | 15 | 1.5 | 2018 | 13 | 0.9 | 2021 | 28 | 1.2 | 1.2 | |
| Pediatr Dermatol | 15 | 1.5 | 2018 | 11 | 0.8 | 2021 | 26 | 1.1 | 1.5 | |
| J Am Acad Dermatol | 11 | 1.1 | 2018 | 14 | 1.0 | 2021 | 25 | 1.0 | 13.8 | |
| North Clin Istanb | 10 | 1.0 | 2018 | 12 | 0.8 | 2020 | 22 | 0.9 | 1 | |
| Acta Dermatovenerol Croat | 17 | 1.7 | 2018 | 3 | 0.2 | 2021 | 20 | 0.8 | 0.6 | |
| Contact Dermatitis | 8 | 0.8 | 2018 | 12 | 0.8 | 2021 | 20 | 0.8 | 5.5 | |
| Indian Dermatol Online J | 16 | 1.6 | 2018 | 3 | 0.2 | 2020 | 19 | 0.8 | 1.7 | **0.000*** |
| Arch Dermatol Res | 5 | 0.5 | 2018 | 13 | 0.9 | 2021 | 18 | 0.7 | 3 | |
| J Dtsch Dermatol Ges | 11 | 1.1 | 2018 | 7 | 0.5 | 2020 | 18 | 0.7 | 3.6 | |
| Turk J Pediatr | 9 | 0.9 | 2018 | 9 | 0.6 | 2021 | 18 | 0.7 | 0.7 | |
| J Cosmet Laser Ther | 13 | 1.3 | 2018 | 4 | 0.3 | 2021 | 17 | 0.7 | 1.2 | |
| Skin Appendage Disord | 5 | 0.5 | 2018 | 12 | 0.8 | 2021 | 17 | 0.7 | 1 | |
| Ann Dermatol | 12 | 1.2 | 2019 | 5 | 0.4 | 2021 | 17 | 0.7 | 1.6 | |
| Dermatol Surg | 10 | 1.0 | 2018 | 6 | 0.4 | 2021 | 16 | 0.7 | 2.4 | |
| Br J Dermatol | 9 | 0.9 | 2018 | 6 | 0.4 | 2021 | 15 | 0.6 | 10.3 | |
| Cutis | 9 | 0.9 | 2018 | 6 | 0.4 | 2021 | 15 | 0.6 | 1.6 | |
| Skinmed | 7 | 0.7 | 2018 | 6 | 0.4 | 2021 | 13 | 0.5 | 0.14 | |
| SkinRes Technol | 5 | 0.5 | 2019 | 6 | 0.4 | 2021 | 11 | 0.5 | 2.2 | |
| Med Bull Şişli Etfal Hosp | 4 | 0.4 | 2018 | 9 | 0.6 | 2020 | 13 | 0.5 | 1.2 | |
| J Cutan Pathol | 5 | 0.5 | 2018 | 9 | 0.6 | 2021 | 14 | 0.6 | 1.7 | |
| J Cutan Med Surg | 8 | 0.8 | 2018 | 4 | 0.3 | 2021 | 12 | 0.5 | 2.3 | |
| Int Ophthalmol | 4 | 0.4 | 2017 | 6 | 0.4 | 2022 | 10 | 0.4 | 1.6 | |
| Int Wound J | 10 | 1.0 | 2019 | 1 | 0.1 | 2020 | 11 | 0.5 | 3.1 | |
| Int J Rheum Dis | 5 | 0.5 | 2017 | 7 | 0.5 | 2020 | 12 | 0.5 | 2.5 | |
| Arch Rheumatol | 9 | 0.9 | 2018 | 4 | 0.3 | 2021 | 13 | 0.5 | 1.1 | |
| Am J Dermatopathol | 9 | 0.9 | 2018 | 3 | 0.2 | 2021 | 12 | 0.5 | 1.1 | |
| Allergy | 3 | 0.3 | 2018 | 10 | 0.7 | 2021 | 13 | 0.5 | 12.4 | |
| Other | 343 | 34.8 | | 348 | 24.5 | | 691 | 28.7 | | |
| Total | | | | | | | 2406 | 100.0 | | |

*$P < 0.05$, **The year with the highest number of dermatology papers from Turkey

**Table 3. The distribution of article subjects in two exemplary journals in which the frequency of dermatology publications from Turkey has increased (Dermatologic Therapy) and decreased (Indian Journal of Dermatology, Venereology and Leprology)**

| | Dermatologic therapy | | Indian Journal of Dermatology, Venereology, and Leprology | | *P* value |
|---|---|---|---|---|---|
| **Subjects** | **Frequency** | **%** | **Frequency** | **%** | |
| Acne | 7 | 2.56% | | | |
| Autoimmune bullous | 7 | 2.56% | | | |
| Bacterial | 2 | 0.73% | | | |
| Connective tissue disorders/vasculitides | 10 | 3.66% | | | |
| Cosmetic dermatology | 10 | 3.66% | 1 | 7.14 | |
| COVID-19 | 77 | 28.21% | | | |
| Cutaneous lymphoma | 10 | 3.66% | 2 | 14.29 | |
| Dermatitis | 3 | 1.10% | | | |
| Dermoscopy | 10 | 3.66% | | | |
| Drugs | 21 | 7.69% | | | |
| Fungal | 3 | 1.10% | | | |
| Genodermatoses | 2 | 0.73% | 2 | 14.29 | |
| Hair disorders | 6 | 2.20% | 2 | 14.29 | |
| Hidradenitis suppurativa | 7 | 2.56% | | | |
| Melanoma | 2 | 0.73% | | | |
| Nail disorders | 1 | 0.37% | | | **0.003*** |
| Nevi | 1 | 0.37% | | | |
| Non-melanoma skin cancer | 4 | 1.47% | 1 | 7.14 | |
| Other | 6 | 2.20% | 2 | 14.29 | |
| Other neoplastic diseases | 6 | 2.20% | | | |
| Other papulosquamous diseases | 1 | 0.37% | 1 | 7.14 | |
| Parasitic disorders | 7 | 2.56% | | | |
| Pediatric dermatology | 4 | 1.47% | | | |
| Photodermatology | 2 | 0.73% | | | |
| Pruritus | 2 | 0.73% | | | |
| Psoriasis | 29 | 10.62% | 2 | 14.29 | |
| Psychodermatology | 3 | 1.10% | | | |
| Rosacea | 4 | 1.47% | | | |
| Surgery | 6 | 2.20% | | | |
| Systemic diseases and dermatology | 2 | 0.73% | | | |
| Urticaria | 10 | 3.66% | | | |
| Viral diseases | 5 | 1.83% | 1 | 7.14 | |
| Vitiligo | 3 | 1.10% | | | |
| **Grand total** | **273** | **100.00%** | **14** | **100.00%** | |

*$P < 0.05$

such as quickening peer review procedures and publishing COVID-19-related papers with early and free access options. The journals that were favored by Turkish dermatologists were two of those that changed their publishing policies. Early and free access to articles means earlier and more citations and views, leading to a higher preference by authors for such journals. To prove this hypothesis, we compared Dermatologic Therapy, which comprised 19.3% of the articles produced by Turkish dermatologists in the post-pandemic era, with a journal that had decreased popularity among Turkish dermatologists (Indian Journal of Dermatology, Venereology and Leprology). None of the publications by the latter journal was about COVID-19, the hot topic of the era. Unlike many other scientific journals, the Indian Journal of Dermatology,

Venereology and Leprology did not change its peer-review and publication policy during the pandemic because of the fear of publishing articles of low scientific value or containing misleading information about the newly emerging disease.[3] As of December 2022, both Dermatologic Therapy and the Journal of Cosmetic Dermatology became fully open access, requiring article processing charges from authors. Therefore, we predict that another study conducted within two or three years may demonstrate a substantial decrease in the popularity of these journals among Turkish dermatologists.

### Study limitations

There are a few limitations to this study. First, this was an observational study, and the pre- and post-pandemic groups of publications did not encompass the same amount of time. Although we allowed three more months after the cessation of pandemic conditions in Turkey, there may still be articles that have been submitted but not yet published. Many journals allowed fast-track publishing for COVID-19-related studies, thus withholding studies on other subjects, which may have been the reason for the high percentage of COVID-19-related articles.

## Conclusion

Overall, the COVID-19 pandemic appears to have increased the academic productivity of Turkish dermatologists. The scientific publishing behaviors of dermatologists in Turkey remarkably changed during the pandemic, especially in terms of publication numbers, journals of publication, article types, and subjects of articles. Although COVID-19 is not a primarily dermatologic disease, during the pandemic period, it was the most popular subject among Turkish dermatologists. We believe that this study will guide young dermatologists in planning and publishing their work.

### Ethics

**Ethics Committee Approval:** Since it did not involve patient data, the study was not applicable for ethical board approval.

**Informed Consent:** It wasn't obtained.

### Authorship Contributions

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

**Conflict of Interest:** The authors declared that they have no conflict of interest.

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Orginal Article

# Eosinophil and Monocyte Counts as Hematological Markers for Response to Tetracyclines for Treating Bullous Pemphigoid

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## Abstract

**Aim:** Tetracyclines are used in bullous pemphigoid (BP) treatment because of their anti-inflammatory properties. We investigated the effects of tetracyclines on blood cell counts, which serve as inflammatory markers, in patients with BP.

**Materials and Methods:** The study included 50 patients with BP who were treated with tetracycline group antibiotics and followed up for an average duration of 3.1±1.2 months in a university hospital between January 2013 and December 2022. Demographic data, comorbidities, medications, physical examination findings, treatment responses, and hematological parameters before and after treatment were retrospectively recorded.

**Results:** The median blood eosinophil count (450 cells µL-1; range: 0-430) and the mean blood monocyte count (660 cells µL-1; range: 300-1100) of the 50 patients with BP were significantly higher than those of the healthy age- and gender-matched Turkish population ($P < 0.001$; $P = 0.01$; respectively). At the end of the follow-up period, 30 patients were in remission, whereas relapses occurred in 20 patients. The eosinophil and monocyte cell count, eosinophil-to-lymphocyte ratio (ELR), and C-reactive protein (CRP) levels in patients who were in remission were significantly lower compared to those pre-treatment ($P = 0.001$, $P = 0.02$, $P < 0.001$, $P = 0.001$, respectively). There was no significant difference between the doxycycline and tetracycline treatment groups regarding the odds of remission after treatment [odds ratio: 2 (95% confidence interval: 0.5-7.3)].

**Conclusion:** Higher levels of circulating monocytes indicate their role in the pathogenesis of BP. Peripheral eosinophil count, ELR, and monocyte count, along with CRP, could serve as markers for monitoring the response to tetracyclines and the risk of relapse in patients with BP.

**Keywords:** Eosinophil and monocyte count, anti-inflammatory effect, bullous pemphigoid, hematological parameters, tetracycline group antibiotics

## Introduction

Bullous pemphigoid (BP), the most common autoimmune blistering skin disease, is characterized by autoantibodies against the hemidesmosomal proteins BP180 and BP230. Recent studies have indicated a 2-to 4-fold increase in the incidence of BP.[1,2] A multicenter study in Turkey has estimated that the incidence of pemphigoid diseases increases with age, with an overall incidence rate of 3.55 cases per 1,000,000.[3] The clinical presentation is characterized by itchy urticarial plaques and tense bullae on the trunk and extremities although some patients may only experience itching. The disease predominantly affects the elderly population.[4]

According to the European guidelines, the recommended first-line treatment for mild, moderate, and severe pemphigoid disease includes superpotent topical corticosteroids applied to the entire body at 20-40 g/day. In severe cases, oral prednisolone is the standard treatment. Alternatives to prednisolone treatment include agents such as azathioprine, mycophenolate mofetil, dapsone, doxycycline, methotrexate, and mycophenolate mofetil, either alone or in combination with oral corticosteroids.[5]

Tetracyclines are broad-spectrum antibiotics that inhibit protein synthesis at the ribosomal stage.[6] Beyond their antimicrobial

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effects, they have biological effects on inflammation, proteolysis, angiogenesis, apoptosis, metal chelation, ionophoresis, inhibition of immunoglobulin E (IgE) synthesis, and bone metabolism. Therefore, their use in rosacea, bullous dermatoses, neutrophilic disorders, pyoderma gangrenosum, sarcoidosis, aortic aneurysm, metastatic cancer, periodontitis, and rheumatoid arthritis has been explored.[7] Doxycycline has also been reported to inhibit leukocyte chemotaxis, reduce the release of inflammatory cytokines, and decrease the production of pathogenic nitric oxide.[8] Tetracyclines are used in BP treatment for their anti-inflammatory properties.[9]

A multicenter, parallel group randomized controlled trial demonstrated that doxycycline was not inferior to oral prednisolone concerning the effectiveness and safety in the long term.[9] However, the effects of tetracyclines on blood cells in patients with BP remain unknown. Inexpensive, non-invasive, and easily applicable hematological parameters have been used as new inflammatory markers in various inflammatory, cardiovascular, and malignant diseases.[10] This study aimed to evaluate the effect of tetracyclines on blood cell counts serving as inflammatory markers in patients with BP.

## Materials and Methods

The study included 50 patients with BP treated with tetracycline group antibiotics and followed up in a specialized outpatient clinic for autoimmune blistering diseases in a university hospital between January 2013 and December 2022. The diagnosis of pemphigoid was established with the clinical presence of tense vesiculobullous, urticarial lesions and/or nodular lesions with excoriated surfaces, observation of a subepidermal blister with eosinophils in both the blister cavity and dermis on histological examination, and the presence of linear C3 ± IgG accumulation in the basal membrane zone on direct immunofluorescence examination. Patients with active infection or malignancy or those receiving systemic steroids and other immunosuppressive treatments were excluded from the study. The baseline disease severity of patients was determined on the basis of the involvement of body surface area.[11] The involvement of less than 10% of the body surface area was considered mild, 10-30% moderate, and more than 30% severe. The outcome measures used in monitoring BP were based on the recommendations of the international panel published by Murrell et al.[12] In a patient with controlled disease, the appearance of three or more new lesions a month (bullae, eczematous lesions, urticarial plaques) that do not heal spontaneously in one week, extension of existing lesions, or daily complaints of pruritus were considered as relapse. Twenty-six patients were started on 2x200 mg/day doxycycline, while 24 patients were received 4x500 mg tetracycline treatment. In addition, all patients were administered superpotent topical corticosteroid treatment from the first day of therapy.

Demographic data, comorbidities, medications, physical examination findings, treatment responses, hematological parameters before and after the treatment; neutrophil, lymphocyte, monocyte, platelet, eosinophil counts, and red cell distribution width, mean platelet volume (MPV), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and remission status at the end of the treatment were retrospectively recorded from the patient files. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and eosinophil-to-lymphocyte ratio (ELR) were calculated from these parameters. Complete blood count was measured using the Beckman Coulter DxH 800 with impedance method features. CRP was determined using the Beckman Coulter AU 5800, which is capable of turbidimetric testing. The ESR was determined using photometric capillary flow kinetic analysis with the ALIFAX test 1 device.

Clinical data were evaluated after the approval of the Dokuz Eylül University Non-interventional Research Ethics Committee (approval number: 2022/42-01, date: 28.12.2022). Because of the retrospective nature of the study, informed consent of the patients was not required.

### Statistical analysis

Data obtained at the end of the research were analyzed using the "Statistical Package for Social Sciences for Windows 24.0" program. Descriptive statistics were used to present the demographic and clinical characteristics of the study subjects. The normality of the continuous variables was evaluated using the Shapiro-Wilk test. The Wilcoxon test was used to compare the measurements of dependent groups, and the Mann-Whitney U test was used for independent groups. Independent samples t-test and Mann-Whitney U test were used to determine whether the blood monocyte and eosinophil counts of patients with BP differed from those of the healthy, age- and gender-matched Turkish population. All statistical tests were two-tailed, and a p value of less than 0.05 was considered statistically significant.

## Results

The study included 33 women (66%) and 17 men (34%) with BP. The mean age was 70.9±13.2 years (range: 31-92 years). Patients were followed up for an average duration of 3.1±1.2 months (follow-up range: 2-8 months) after the initiation of tetracycline-class antibiotics. Fifty percent of the patients had moderate disease severity, whereas the other 50% had severe disease. Oral mucosal involvement was observed in

42% of the patients. The most frequent systemic disorders were hypertension (n = 36, 72%), diabetes mellitus (n = 28, 56%), coronary artery disease (n = 14; 28%), and kidney failure (n = 7; 14%). Alzheimer's disease was observed in 14% of the patients, and Parkinson's disease was observed in 4% of the patients. Diuretics were the most common drugs associated with pemphigoid and were used by 44% (n = 22) of the patients. A comparison of the rates of patients taking pemphigoid-associated drugs between the groups with remission and relapse is given in Table 1. During the treatment period, gastrointestinal irritation was the most common side effect (n = 12, 24%) observed in the patients, followed by an increase in transaminations (n = 10, 20%) and oral candidiasis (n = 5, 10%).

At the end of the follow-up period, 30 patients (60%) receiving tetracycline-class antibiotics were in remission, whereas relapses occurred in 20 patients (40%). The pre- and post-treatment hematological parameters of the patients are presented in Table 2. When hematological parameters were evaluated in the entire patient group, it was determined that there was a statistically significant decrease in eosinophil count, ELR, and CRP values at the end of the treatment period compared to pre-treatment ($P = 0.001$; $P < 0.001$; $P = 0.002$, respectively). After treatment, a significant decrease was observed in the eosinophil count, ELR, and CRP values in both the doxycycline and tetracycline groups.

The median blood eosinophil count of the 50 patients with BP (450 cells $\mu L^{-1}$; range: 0-430) was significantly higher ($P < 0.001$) than that of the healthy age- and gender-matched Turkish population (100 cells $\mu L^{-1;}$ range: 0-140). Compared with the same control group (560±180 cells $\mu L^{-1}$; range: 200-1000), the mean blood monocyte count of the patients with BP (660±180 cells $\mu L^{-1}$; range: 300-1100) was significantly higher ($P = 0.01$).

No significant difference was observed between the remission and relapse groups regarding basal eosinophil and monocyte

**Table 1. Comparison of the rate of patients taking pemphigoid-associated drugs between the remission and relapse groups**

| Drugs associated with pemphigoid | Group with remission, (n = 30) | Group with relapse, (n = 20) | *P* |
|---|---|---|---|
| Likely or probable association, n (%) | | | |
| Gliptins | 6 (20) | 3 (15) | |
| Aspirin | 7 (23.3) | 0 | |
| Furosemide + hydrochlorothiazide | 16 (53.3) | 6 (30) | |
| Losartan + lisinopril | 14 (46.7) | 7 (35) | |
| Total number of patients taking pemphigoid-associated drugs (%) | 20 (66.7) | 7 (35) | 0.028* |

*Pearson chi-square

**Table 2. Comparison of hematological parameters of the patients between the pre and post-treatment**

| Haematological parameters | Pre-treatment Mean (range) | Post-treatment Mean (range) | *P** |
|---|---|---|---|
| Hemoglobin | 12 (7.5-15.1) | 12.7 (7.9-15.4) | 0.01 |
| MCV | 86 (63.2-106.1) | 87 (67-100) | 0.7 |
| Neutrophil count ($10^3/\mu L$) | 5.2 (2.2-25.9) | 4.8 (0.8-22) | 0.80 |
| Lymphocyte count ($10^3/\mu L$) | 1.6 (0.7-9) | 1.6 (0.3-3.4) | 0.64 |
| Eosinophil count ($10^3/\mu L$) | 0.4 (0-4.3) | 0.2 (0-2.6) | **0.001** |
| Monocyte count ($10^3/\mu L$) | 0.7 (0.3-1.10) | 0.6 (0.3-1.1) | 0.083 |
| Platelet count ($10^3/\mu L$) | 267 (137-637) | 255 (140-437) | 0.58 |
| RDW (%) | 15 (12.7-22.6) | 15.2 (13-23) | 0.13 |
| NLR | 3 (0.6-11.3) | 2.9 (0.5-44.6) | 0.67 |
| MLR | 0.4 (0.06-1) | 0.3 (0.1-2.6) | 0.31 |
| PLR | 181 (30-420) | 178 (79-933) | 0.81 |
| ELR | 0.3 (0-1.4) | 0.1 (0-2.6) | **0.000** |
| MPV | 8.4 (6.6-11.6) | 8.4 (6.8-11.8) | 0.44 |
| CRP (mg/dL) | 12.6 (0.3-92.5) | 5.7 (0.2-188) | **0.002** |
| ESH (mm/h) | 23.5 (2-77) | 20 (2-76) | 0.176 |

*Wilcoxon signed-rank test, MCV: Mean corpuscular volume, RDW: Erythrocyte distribution width, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

counts ($P$ = 0.773, $P$ = 0.6; respectively). No significant difference was found in eosinophil counts between patients with moderate and severe BP ($P$ = 0.81), and no correlation was observed (r=-0.03; $P$ = 0.8).

A comparison of the hematological parameters according to groups with remission and relapse is given in Table 3. At the end of the treatment period, the eosinophil and monocyte cell counts, ELR, and CRP levels in patients who were in remission were significantly lower compared to pre-treatment ($P$ = 0.001, $P$ = 0.02, $P$ < 0.001, $P$ = 0.001, respectively). In the group with relapse, no significant statistical difference was found in these values compared to pre-treatment (respectively; $P$ = 0.18, $P$ = 0.94, $P$ = 0.94, $P$ = 0.35). There was no significant difference between the doxycycline and tetracycline treatment groups in terms of the odds of remission after treatment [odds ratio: 2 (95% confidence interval: 0.5-7.3)] (Table 4).

## Discussion

In our study, the median basal peripheral eosinophil count in BP patients was significantly higher than that in healthy age- and gender-matched control groups. Approximately 50-60% of BP patients have peripheral eosinophilia in previous studies.[13,14] The presence of tissue and blood eosinophilia is one of the prominent findings in BP and is associated with inflammatory skin findings such as eczema and urticaria-like skin lesions. Moreover, eosinophils have been suggested to be the main source of the cytokine interleukin-31 (IL-31), which plays a key role in itch-related inflammation in BP.[15]

**Table 3. Comparison of pre- and post-treatment hematological parameters in patients in remission and relapse**

| | Group with remission, n = 30 Mean (range) | | *P* | Group with relapse, n = 20 Mean (range) | | *P** |
|---|---|---|---|---|---|---|
| Haematolological parameters | Pre-treatment | Post-treatment | | Pre-treatment | Post-treatment | |
| Hemoglobin | 12 (7.5-15) | 12 (8.3-15) | 0.15 | 12 (10-15) | 13 (7.9-15) | 0.002 |
| MCV | 87 (63-98) | 88 (68-100) | 0.76 | 85 (78-106) | 85 (75-99) | 0.185 |
| Neutrophil count ($10^3$/µL) | 5.3 (2.2-16) | 4.8 (2.7-9) | 0.41 | 5.2 (3.2-11) | 4.8 (0.8-22) | 0.49 |
| Lymphocyte count ($10^3$/µL) | 1.6 (1-9) | 1.7 (0.9-3.4) | 0.95 | 1.7 (0.7-3) | 1.6 (0.3-3) | 0.35 |
| Eosinophil count ($10^3$/µL) | 0.4 (0-2.6) | 0.2 (0-1.2) | **0.001** | 0.4 (0-4.3) | 0.2 (0-2.6) | **0.186** |
| Monocyte count ($10^3$/µL) | 0.7 (0.3-1) | 0.5 (0.3-1) | **0.02** | 0.6 (0.3-1) | 0.6 (0.4-1) | **0.948** |
| Platelet count ($10^3$/µL) | 265 (137-637) | 252 (140-437) | 0.45 | 279 (176-423) | 264 (144-421) | 1.0 |
| RDW (%) | 15 (13-22) | 15 (13-23) | 0.34 | 14 (13-18) | 15 (13-18) | 0.225 |
| NLR | 2.8 (0.64-11) | 2.9 (1.1-7.4) | 0.5 | 3.3 (1.3-5.8) | 2.8 (0.5-4.4) | 0.97 |
| MLR | 0.4 (0.06-0.7) | 0.3 (0.1-0.9) | 0.094 | 0.3 (0.2-1) | 0.3 (0.2-2.6) | 0.36 |
| PLR | 185 (30-352) | 169 (85-303) | 0.32 | 181 (89-420) | 181 (79-933) | 0.47 |
| ELR | 0.2 (0-1) | 0.1 (0-1) | **<0.001** | 0.3 (0-1.4) | 0.2 (0-2.6) | **0.94** |
| MPV | 8.6 (6.6-11.6) | 8.5 (6.8-11.8) | 0.93 | 8.1 (7.3-10) | 8.2 (7.2-9.8) | 0.189 |
| CRP (mg/dL) | 13.3 (0.3-81) | 4.7 (0.2-135) | **0.001** | 9 (0.6-92) | 6.5 (2.5-188) | **0.35** |
| ESH (mm/h) | 20 (2-77) | 18 (2-63) | 0.095 | 27 (7-75) | 22 (3-76) | 0.82 |

*Wilcoxon signed-rank test, MCV: Mean corpuscular volume, RDW: Erythrocyte distribution width, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

**Table 4. Characteristics of patients in the treatment groups**

| | Doxycycline (n = 26) | Tetracycline (n = 24) | *P* |
|---|---|---|---|
| Age | 67.5±12.3 (31-86) | 74.6±13.4 (37-92) (ND) | 0.032** |
| **Sex** | | | |
| Female | 15 F | 18 F | 0.19 |
| Male | 11 M | 6 M | |
| Pemphigoid disease severity | Moderate: 11<br>Severe: 15 | Moderate: 13<br>Severe: 11 | 0.57 |
| Oral mucosal involvement | Yes: 9<br>No: 17 | Yes:12<br>No: 12 | 0.27 |
| Remission rate after treatment period; n (%) | 18 (69.2) | 12 (50) | 0.16* |
| OR (95% CI) | 2 (0.5-7.3) | Ref. | |

*$P$ = 0.16 doxycycline versus tetracycline/pearson chi-square, **: Mann-Whitney U test, OR: Odds ratio, CI: Confidence interval, F: Female, M: Male

Gore Karaali et al.[16] have indicated that the eosinophil counts in the blood of patients with BP correlate with disease severity scores. The lack of correlation between eosinophil counts and disease severity in our study may be attributed to our patients consisting only of moderate and severe cases and the inability to retrospectively evaluate the BP area severity index.

In our study, the mean of baseline monocyte values in BP patients was significantly higher compared to the average of healthy control group. This suggests that circulating monocytes play a role in the pathogenesis of BP. BP is characterized by autoantibodies against BP180 and/or BP230, the component proteins of hemidesmosomes that connect basal epithelial cells to the underlying basement membrane. After the binding of autoantibodies to their target antigens, the complement cascade is activated. Subsequently, neutrophils and monocytes/macrophages accumulate at the dermoepidermal junction. These activated inflammatory cells release proteases such as neutrophil elastase and matrix metalloproteinase-9 (MMP-9), which cleave and degrade BP180, thus leading to subepidermal blister formation.[17] de Graauw et al.[18] have shown in an *ex vivo* model that monocytes and neutrophils act synergistically in the formation of dermoepidermal blisters in BP. Riani et al.[19] have noted that monocytes play a role in BP pathogenesis by increasing MMP-9 synthesis via CXCL10 (chemoattractant molecule) with neutrophils. Tetracyclines, especially doxycycline, have MMP inhibitory properties.[20] Another study showed that CCL18 chemokine levels in serum and blister fluid of patients with BP were higher than those in the control group, and in vitro chemotaxis analysis demonstrated that CCL18 triggers the migration of peripheral blood mononuclear cells to BP blister fluid.[21] In BP, CD163+ M2 tissue macrophages detected in increased numbers in lesional skin are responsible for the production of specific chemokines that induce the polarization of helper T cell subgroups. Minocycline, a tetracycline-class antibiotic, reduces the production of CCL22, CCL24, CCL26, and CCL2 from M2 macrophages while not affecting CCL18. On the other hand, the production of CCL18 was found to decrease with dexamethasone and cyclosporine.[22]

Most patients with BP are elderly, often use multiple drugs, and have significant comorbidities such as neurological and cardiovascular diseases, malignancies, and diabetes, making the treatment of BP quite challenging. Systemic corticosteroids can improve symptoms but may lead to numerous side effects, especially with prolonged use, and can even increase mortality rates. There is a need for an alternative treatment that can rapidly alleviate symptoms and maintain long-term remission while avoiding or minimizing the side effects of systemic corticosteroids.[23] Studies have reported that tetracycline group antibiotics are safer and similar to systemic prednisolone therapy in controlling the disease.[7,9,24]

In our study, 60% of patients with BP treated with tetracycline-class antibiotics were still in remission, whereas 40% experienced relapse. A systematic meta-analysis involving 341 patients with pemphigoid found that 77.7% of 148 patients using tetracycline with topical steroids responded to the treatment, but 31.8% experienced relapse.[25] The fact that there were only a limited number of patients with moderate and severe disease in our study may have contributed to the difference in the treatment responses.

In our department, patients' drugs associated with pemphigoid are determined, and if possible, they are stopped or changed. The frequency of patients taking drugs associated with pemphigoid was significantly higher in the remission group than in the relapse group in our study. Molina et al.[26] reported that patients with pemphigoid who continued to use the triggering drug more frequently needed immunosuppressive agents to achieve clinical remission. They also had to use them for a longer period. Therefore, withdrawal of the drug may have allowed patients to achieve remission under tetracycline therapy in our study.

In our study, a significant decrease in eosinophil count and ELR was observed in patients treated with tetracycline-class antibiotics compared with pretreatment. Gehring et al.[27] suggested that tetracyclines may be effective in BP by inducing eosinophil apoptosis. In a study evaluating peripheral blood and tissue eosinophil counts in BP patients, high eosinophil counts were associated with relapses and the need for hospitalization. The study indicated that peripheral eosinophil count could be used to monitor treatment response and identify relapse risk early.[16] The significant decrease in eosinophil counts in patients in remission in our study supports these findings.

As a different finding, a significant decrease in peripheral blood monocyte count was observed in the group continuing in remission after tetracycline treatment in our study. The significant reduction in monocyte count in the remission group suggests that monocyte levels can be an indicator of disease activity and the formation of relapse in addition to eosinophil counts. It has been shown that high anti-BP180 ELISA autoantibody titers in monitoring disease activity in BP is a good indicator of relapse.[28] However, these tests are expensive and not readily available, limiting their routine use. Hematological parameters, which are quick, easily accessible, and inexpensive tests, are used as inflammation markers in many diseases.

In our study, a significant decrease in CRP levels was observed in the group continuing in remission compared with the baseline value. In contrast, no significant change was detected in the relapsed group. Similarly, Sahin et al.[29] have identified

a significant decrease in MPV, peripheral eosinophil count, ESR, and CRP levels during the remission phase compared with the active phase in patients with BP. However, that study did not specify which treatments patients received or whether they were still undergoing any treatment. CRP is an acute-phase protein synthesized in the liver following stimulation by various inflammatory cytokines, including IL-6, IL-1, and tumor necrosis factor (TNF).[30] In BP patients, serum levels of IL-6 and TNF were found to be higher than those in the control group and correlated with lesion numbers and CRP levels.[31]

In our study, no significant statistical difference was observed when comparing the remission likelihood ratios between the tetracycline and doxycycline treatment groups. Systematic meta-analysis data showed that the patient response rate to tetracycline was statistically higher than that to doxycycline and minocycline.[25]

### Study limitations

The limitations of our study include a small sample size, lack of a control group, its retrospective nature, and the fact that all subjects were from a single center. It was not possible to evaluate the efficacy of tetracycline therapy alone because patients received topical potent corticosteroid therapy in combination with tetracycline-class antibiotics. Anti-BP180 and anti-BP230 ELISA autoantibodies were not studied in patients with BP. Despite these limitations, our study has identified for the first time that peripheral blood monocyte counts are higher in patients with BP than in the healthy age- and gender-matched control group and significantly decrease in the group continuing in remission after treatment.

## Conclusion

In conclusion, in patients with BP, peripheral blood monocyte and eosinophil counts were higher than the average/median of the healthy control group. After treatment with tetracyclines, a significant decrease in eosinophil and monocyte counts and CRP levels was observed only in the remission group. The frequency of previous drug use associated with pemphigoid was higher in the remission group than in the relapse group, indicating that withdrawal of these drugs is necessary for disease control. Tetracycline-class antibiotics are preferred in BP treatment because of their lower frequency of side effects and anti-inflammatory properties. Peripheral eosinophil count, ELR, and monocyte count, along with CRP, could serve as markers for monitoring the response to tetracyclines and the risk of relapse in patients with BP. Further studies with a larger patient series and control groups are needed to confirm these results and evaluate responses to other treatments.

### Ethics

**Ethics Committee Approval:** Clinical data were evaluated after the approval of the Dokuz Eylül University Non-interventional Research Ethics Committee (approval number: 2022/42-01, date: 28.12.2022).

**Informed Consent:** Because of the retrospective nature of the study, informed consent of the patients was not required.

### Authorship Contributions

Concept: C.A., Ö.G., S.A., Ş.A., Design: C.A., Ö.G., S.A., Ş.A., Data Collection or Processing: C.A., Ö.G., S.A., Ş.A., Analysis or Interpretation: C.A., Ö.G., S.A., Ş.A., Literature Search: C.A., Ö.G., S.A., Ş.A., Writing: C.A., Ö.G., S.A., Ş.A.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

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# Eruptive Vellus Hair Cysts Manifesting as Type 1 Segmental Mosaicism

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## Dear Editor,

I read with interest the outstanding case recently published in the Turkish Journal of Dermatology.[1] Poddar et al.[1] reported eruptive vellus hair cysts (EVHC) arranged in a segmental distribution, namely in S-shaped bands respecting the midline. The authors define such a pattern as "zosteriform". Instead, the lesions seem to clearly follow Blaschko lines, which are a known phenotypical pattern of cutaneous mosaicism and the only one followed by mosaic conditions affecting the pilosebaceous unit (e.g. nevus comedonicus). Only two cases of lateralized EVHC have been reported previously,[2,3] but their distribution of lesions is not compatible with segmental mosaicism. Hence, this is the first reported instance of mosaic EVHC.

EVHC can arise sporadically or may be inherited in an autosomal dominant fashion with incomplete penetrance;[4] the genetic defect has not yet been identified. In autosomal dominant skin disorders, heterozygosity for a postzygotic new mutation is defined as type 1 segmental mosaicism.[5] Hence, the case of Poddar et al.[1] allows the inclusion of EVHC among the ever-growing list of conditions known to possibly manifest as type 1 segmental mosaicism.

## Ethics

**Informed Consent:** It wasn't obtained.

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

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# Repair of a Medial Cheek Skin Defect with an Island Pedicle Flap

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## Dear Editor,

The island pedicle flap (IPF), or V-Y advancement flap, is a highly versatile repair method used in subcutaneous adipose tissue-rich areas of the face, including the nasolabial fold, upper lip, and cheek.[1] The term "island pedicle" is preferred because the flap is completely dissected from the surrounding skin and receives its vascular supply from the central subcutaneous part (Figure 1). IPF is relatively simple to design and operate. It is also more mobile than other advancement flaps because there are no dermal or epidermal connections.[2] In this report, we emphasize the use of IPF in dermatologic surgery through a case of basal cell carcinoma in the medial cheek.

A 72-year-old man presented with a 1.5x2 cm biopsy-confirmed basal cell carcinoma. The lesion was located in the left medial cheek adjacent to the nasolabial fold (Figure 2A). After determining the appropriate surgical margins, we decided to repair the defect with IPF because the area was rich in subcutaneous fat and the incision lines could be hidden in the nasolabial fold (Figure 2B). The flap was designed in a V-shape with a peak angle of 30°. Before the operation, written informed consent was obtained from the patient. The procedure started with infiltration anesthesia and the removal of the lesion (Figure 3A, B). After tumor removal, hemostasis was achieved with electrocautery (Figure 3C, D). The flap was then created by incising through the epidermis and dermis to the subcutaneous fat along the designed V-shape (Figure 3E-H). Wide undermining using scissors was performed around the flap (Figure 3I, J). The proximal and distal edges of the flap were also sufficiently dissected to allow mobilization (Figure 3K, L). Narrowing the island pedicle allows greater

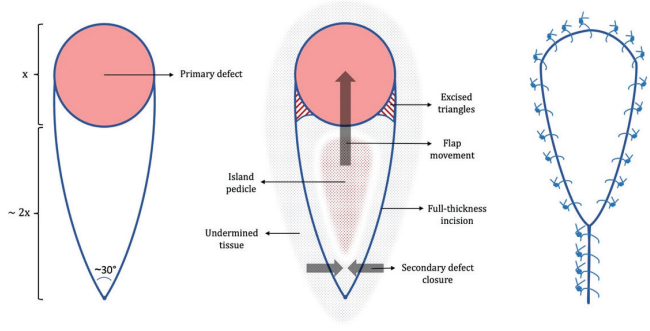


**Figure 1.** Schematic illustration of the IPF procedure. (A) Design of the V-shaped flap. (B) Movement of the flap and preservation of the vascular island pedicle. (C) Final Y-shaped suture lines
IPF: Island pedicle flap

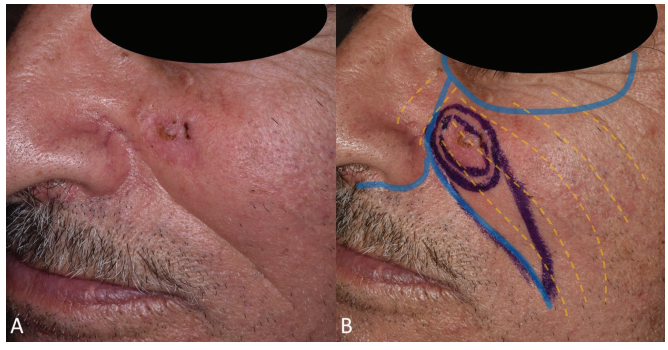


**Figure 2.** (A) Clinical appearance of the lesion before surgery. (B) The upper incision was aligned parallel to the skin tension lines (dotted yellow lines), and the medial and lower incisions were placed along the natural creases (bold blue lines)

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mobilization but also risks vascular supply. Therefore, care was taken to preserve sufficient vascular base. After achieving the desired mobility, the flap was easily moved into the primary defect without any tension (Figure 3M, N). The corners of the flap were rounded at this stage to better fit into the circular defect. Finally, the flap was fixed in place with subcutaneous sutures, and the procedure was completed by placing epidermal sutures (Figure 3O, P). The final suture lines appeared as a Y-shape. No complications occurred, and the scar became almost invisible at a 3-month postoperative period (Figure 4A, B).

IPF is a frequently used flap in dermatological surgery and has several advantages. First, the design of the flap is simple and does not require complex measurements. The color and texture compatibility are excellent because the donor site is adjacent to the defect. The blood supply is robust, and the flap is viable as long as the vascular pedicle is preserved. The lack of skin attachments significantly increases the mobility of the flap.[3] Finally, it has been shown that repairing medial cheek defects with IPF provides reliable functional and cosmetic results.[4] In conclusion, IPF remains a viable option for the repair of medial cheek skin defects.

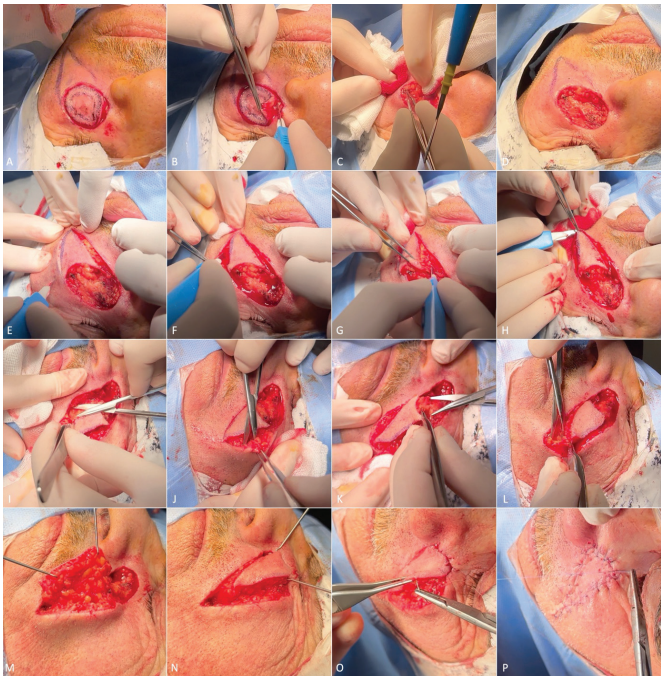

**Figure 3.** Stages of the IPF procedure. (A-D) Removal of the tumor and hemostasis with electrocautery. (E-H) Full-thickness incision deep into the subcutaneous fat. (I-L) Wide undermining around the flap and release of the proximal and distal edges. (M-P) Sliding of the flap into the defect and layered closure

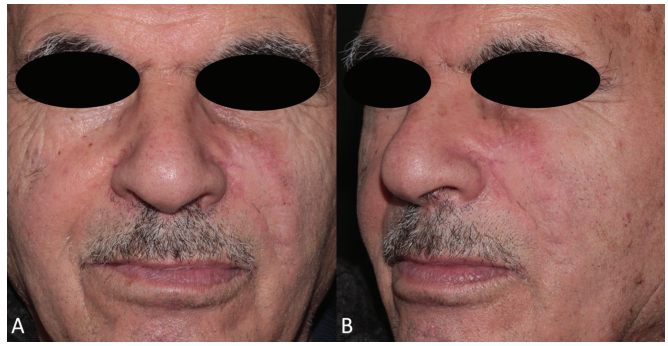

**Figure 4.** Clinical appearance at the postoperative 3rd month. (A) Anterior and (B) oblique views show minimal scarring and no distortion

## Ethics

**Informed Consent:** Before the operation, written informed consent was obtained from the patient.

## Authorship Contributions

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

**Conflict of Interest:** The authors declared that they have no conflict of interest.

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