Original Article

Cutaneous Squamous Cell Carcinoma: A Type of Cancer that Discriminates Against Young Adults

Kutanöz Skuamöz Hücreli Karsinom: Genç Yetişkinlere Karşı Ayrımcı Bir Kanser Türü

Zeynep Gülsüm Güç[1], Hasan Güç[2]

[1]Department of Medical Oncology, Izmir Katip Çelebi University, Atatürk Training and Research Hospital, Izmir, Turkey
[2]Department of Plastic, Reconstructive and Aesthetic Surgery, Tepecik Training and Research Hospital, Izmir, Turkey

ABSTRACT

Introduction: Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers. Young adult cSCC is rare and its clinical features, outcomes, and iatrogenic risk factors are not well defined. This study aimed to specify the clinical characteristics, potential risk factors, and the factors affecting recurrence associated with cSCC in young adults.

Materials and methods: Forty-three patients aged <35 years at diagnosis, who allowed their data to be retrospectively analyzed, and whose full medical history and records were available were included in the study. Their demographic characteristics, date of diagnosis, localization of lesion, pathological and family histories were recorded

Results: Patients' mean age at diagnosis was 29 (17-34) years. Twenty patients (46.5%) had familial history of malignancy; 19 (44.2%) had precancerous lesions before SCC diagnosis. Three (7%) had a history of organ or allogeneic bone marrow transplantation and long-term use of immunosuppressants, three (7%) had genetic predisposition to cutaneous cancers, and three (7%) had a history of RT-CT. Eighteen patients (41.9%) had relapses during the 58-month follow-up. Histopathologically, presence of moderately-poorly differentiated squamous cell carcinoma, prolonged use of immunosuppressants, and history of RT-CT were statistically significantly associated with relapse ($p<0.05$). Kaplan-Meier analysis done for factors affecting survival showed a relationship between survival and presence of genetic risk, poor differentiation, and recurrence ($p<0.05$).

Discussion: Recognizing the risk factors for cSCC in young adults (long-term immunosuppressants, chemoradiotherapy, genetic cutaneous cancer predisposition syndromes, presence of precursor lesions) bear great importance in providing appropriate guidance to ensure early diagnosis and effective treatment.

Keywords: cutaneous squamous cell carcinoma, chemotherapy, radiotherapy, immunosuppressants, genetics

ÖZET

Giriş: Kutanöz skuamöz hücreli karsinom(cSCC) en sık görülen kanserlerden biriyken, genç erişkin cSCC nadirdir ve klinik özellikleri, sonuçları ve iyatrojenik risk faktörleri iyi tanımlanmamıştır. Bu çalışmada genç erişkinlerde cSCC ile ilişkili klinik özellikleri, potansiyel risk faktörlerini ve nüksü etkileyen faktörleri tanımlamak amaçlanmıştır.

Gereç ve yöntemler: Tanı yaşı <35 olan, tam tıbbi öyküsüne ve kullandığı ilaçlara ulaşılabilen ve retrospektif analize izin veren 43 hasta çalışmaya dâhil edildi. Hastaların demografik özellikleri, tanı tarihleri, lezyon lokalizasyonları, patoloji sonuçları ve aile öyküleri kaydedildi.

Bulgular: Çalışmaya dâhil edilen hastaların ortalama tanı yaşı 29 (17-34) yıl olarak bulundu. 20 hastanın (46,5%) ailesinde malignite öyküsü bulunmaktaydı. 19 hastada (44,2%) SCC tanısından önce prekanseröz lezyon saptandığı görüldü. Hastaların %7'sinde organ veya allojenik kemik iliği nakli ve

First Received: 06.07.2022, Accepted: 17.08.2022 doi: 10.5505/aot.2023.61582

uzun dönem immünsupresan kullanımı, %7'sinde kutanöz kanserlere genetik yatkınlık ve %7'sinde RT-KT öyküsü mevcuttu. 58 aylık takip süresinde 18 hastanın (41,9%) nüks ettiği gözlendi. Histopatolojik olarak orta-kötü differansiye skumaöz hücreli karsinom varlığının, uzamış immünsupresan kullanımının, radyoterapi ve kemoterapi öyküsü bulunmasının nüks gelişimi ile istatistiksel anlamlı ilişkisi olduğu gözlendi ($p<0,05$). Sağkalımı etkileyen faktörler için yapılan Kaplan-Meier analizinde genetik risk varlığının, kötü differansiyasyonun ve nüks varlığını sağkalım ile ilişkisi gösterilmiştir. ($p<0.05$)

Tartışma: Genç erişkinlerde uzun süreli immünsupresan kullanımı, kemoradyoterapi, genetik kutanöz kanser yatkınlık sendromları ve prekürsör lezyon varlığı gibi cSCC gelişimi için risk faktörlerinin tanınması uygun danışmanlık, erken tanı ve etkin tedavi sağlamak için büyük önem taşımaktadır.

Anahtar kelimeler: Kutanöz skuamöz hücreli karsinom, kemoterapi, radyoterapi, immünsupresan, genetik

Introduction

Skin cancer is the most common type of malignancy. There is a remarkable increase in its incidence across the world with about 3.5 million new diagnoses each year in the USA alone. Its most lethal subtype is malignant melanoma. Although non-melanoma skin cancers (NMSCs) show lower mortality rates, lesions usually are locally aggressive, can lead to disorders, have extremely negative effects on quality of life, and incur significant healthcare costs.

Cutaneous squamous cell carcinoma (cSCC) is a keratinocyte-derived skin cancer which predominantly affects older people [1]. The main etiological factor for cSCC is ultraviolet radiation (UVR) from the sun. Its risk factors and etiology in young adults, however, are different. Cases of cSCC have been reported in young adults with hereditary and congenital conditions such as various tumor syndromes, photosensitivity disorders, and birthmarks [2,3,4]. Long-term immunosuppression, radiotherapy and voriconazole therapy have also been identified as iatrogenic risk factors for cSCC [5,6,7]. Given the growing number of long-term survivors of childhood cancers and other chronic medical conditions, cases of young adult NMSCs caused by iatrogenic risk factors are estimated to be more common than previously reported. Failure to recognize these risk factors may lead to delays in diagnosis and increased tumor burden.

In this study we aimed to identify among our cSCC patients those who were diagnosed in young adulthood and define their clinical and pathological characteristics. We further aimed to determine their risk factors and describe the follow-up of cSCC in young adults exposed to these risk factors.

Methods

Patients

The institutional and national research committees' ethical standards, as well as the 1964 Declaration of Helsinki and its later revisions or comparable ethical standards were followed in the study. One-thousand-and-fifty-three patients who were diagnosed with squamous cell carcinoma (SCC) in the period from January 2014 through December 2019 were histopathologically screened. Forty-three patients who were <35 years of age at the time of diagnosis, had allowed their data to be used for retrospective analysis, and whose full medical history and medication records were available were included in the study. Patient data including demographic characteristics, date of diagnosis, localization of lesion, pathology, medical history (e.g., malignancy, stem cell or organ transplantation, genetic syndrome, or presence of other chronic diseases), medication history (focusing on chemotherapeutic and immunosuppressive agents), radiation exposure (total body irradiation [TBI] and cGy localized radiation therapy), and familial history were recorded. Long-term immunosuppression was defined as having received immunosuppressive therapy for more than 6 months.

 Copyright©Ankara Hematoloji Onkoloji Derneği

Statistical analysis

The Statistical Package for Social Sciences for Windows 20.0 (IBM, Armonk NY, USA) was used for analysis. Descriptive statistics summarized frequencies and percentages for categorical, mean, and standard deviation for continuous variables. Categorical variables were compared with the Independent Samples T-test and categorical parameters with the $\chi 2$ test. $p<0.05$ was considered statistically significant.

Results

Of the 43 patients included in the study, 26 (60.5%) were male and 17 (39.5%) were female. Their mean age at diagnosis was 29 (range, 17-34) years. All patients had a histopathologically confirmed diagnosis of cutaneous squamous cell carcinoma. Lesions were most commonly located in the head-neck region (81.4%), followed by the upper extremities (9.3%). Mean follow-up period was 58 (range, 5-138) months.

While all patients had undergone wide local excision, re-surgery was needed in four patients (9.3%) because of surgical borderline positivity. Reconstruction was required in 25 patients (58.1%) after excision because of the location of the lesion and the size of the defect. Of these 25 patients, flaps were used in 17 and grafts were used in eight patients. Demographic and clinical characteristics of the patients are given in Table 1.

Review of patients based on their medical and familial histories revealed that 20 (46.5%) had a familial history of (pathologically confirmed) malignancy, and precancerous lesions were detected in 19 (44.2%) before their SCC diagnosis. Of the precancerous lesions, 12 (27.9%) were recorded as kerato-acanthoma, four (9.3%) as Bowen's disease, and three (7%) as burn scar.

Three (7%) of 43 patients underwent genetic analysis due to their clinical conditions; two were diagnosed with xeroderma pigmentosum and one was diagnosed with Gorlin's syndrome. One patient had a history of hematopoietic stem cell transplant due to leukemia in the pediatric period and received a high dose of chemotherapy. The patient had received long-term immunosuppressant therapy for Graft versus Host Disease (GvHD) and was continuing to use it at the time of diagnosis. Two patients had a history of concomitant definitive chemoradiotherapy to the loco-regional area for nasopharyngeal cancer.

Of the three (7%) patients with a history of long-term immunosuppressive use, one is the above-mentioned patient who had been taking immunosuppressants due to GvHD after allogeneic bone marrow transplantation. This

Table 1. Demographic and clinical characteristics of patients

Parameters	Number of patients (%)
Gender	
Female	17 (39.5%)
Male	26 (60.5%)
Histopathological Subtype	
Acantholytic	8 (18.6%)
Keratoacanthomatous	6 (14.0%)
Unspecified	29 (67.4%)
Grade	
Well differentiated	22 (51.2%)
Moderately / Poorly differentiated	21 (48.8%)
Lymph Node Involvement	
No	38 (88.4%)
Yes	5 (11.6%)
Localization	
Head-Neck	35 (81.4%)
Upper extremity	4 (9.3%)
Torso	2 (4.7%)
Lower extremity	2 (4.7%)
Reconstruction	
Not Done	18 (41.9%)
Flap	17 (39.5%)
Graft	8 (18.6%)
Familial History of Malignancy	
No	23 (53.5%)
Yes	20 (46.5%)
Precancerous Lesion	
Keratoacanthoma	12 (27.9%)
Bowen's	4 (9.3%)
Burn scar	3 (7.0%)
No	24 (55.8%)
Recurrence	
Yes	18 (41.9%)
No	25 (58.1%)
Immunosuppression	
Yes	3 (7.0%)
No	40 (93.0%)
Radiotherapy	
Yes	3 (7.0%)
No	40 (93.0%)
Chemotherapy	
Yes	3 (7.0%)
No	40 (93.0%)

Copyright©Ankara Hematoloji Onkoloji Derneği

Table 2. Relationship between clinical and pathologic factors and recurrence

	Recurrence		
	No	Yes	*p*-value
Gender			
Male	16	10	0.403
Female	9	8	
Grade			
Well Differentiated	17	5	**0.01***
Moderately/Poorly Differentiated	8	13	
Familial History of Malignancy			
No	12	11	0.295
Yes	13	7	
Precancerous Lesion			
No	17	7	0.056
Yes	8	11	
Localization			
Head-Neck	23	12	0.090
Other	2	4	
Surgical Margin			
Negative	24	15	0.158
Positive	1	3	
Use of immunosuppressants			
No	25	15	**0.034***
Yes	0	3	
History of Chemotherapy			
No	25	15	**0.034***
Yes	0	3	
History of Radiotherapy			
No	25	15	**0.034***
Yes	0	3	
Genetic Diagnosis			
No	25	15	**0.034***
Yes	0	3	

* statistically significant

patient was taking high doses of steroids and cyclosporine. The patient was also given voriconazole for fungal infection in the post-transplant period. The other two patients were one that had a liver transplantation due to cryptogenic liver cirrhosis, and another that had a kidney transplantation due to renal failure, and both were on long-term immunosuppressants to prevent rejection.

Recurrence was seen in 18 (41.9%) patients in the 58-month follow-up period. Statistical analysis done for the factors affecting recurrence showed that gender, familial history of malignancy, presence of pre-cancerous lesion, lesion localization and surgical margin positivity had no effect on recurrence. Histopathologically, the presence of moderately-poorly differentiated SCC, prolonged use of immunosuppressants, and a history of radiotherapy and chemotherapy were seen to be statistically significantly associated with the development of recurrence($p<0.05$) (Table 2).

Five patients had died in the follow-up period. The Kaplan-Meier analysis for factors affecting survival showed presence of genetic risks, histopathologically moderately-poorly differentiated squamous cell carcinoma and recurrence were all related with survival ($p<0.05$).

Discussion

In our study we aimed to determine the etiological factors and risks for cSCC in young adults and to identify which patients should be vigilantly followed-up for recurrence. cSCCs represent a major health problem worldwide. Although they rarely metastasize, they are often found to be locally invasive at diagnosis and surgical treatments may be insufficient. Identifying and treating the lesions at an early stage, determining its etiological factors, and thereby recognizing which patients should be followed-up for prevention are of great importance.

In our study, 21% of young adult cSCC patients had iatrogenic risk factors including chemotherapy, radiotherapy, long-term immunosuppression, or a combination of these. In about half of these patients, the presence of precancerous lesions before cSCC was histopathologically confirmed. The most common precancerous lesion was kerato-acanthoma. In a study by Huang et al. [8], 29% of the 124 young adult non-melanoma cutaneous malignancy patients had similar risk factors. Similarly, previous studies have shown that the risk of NMSC increased in adult patients after HSCT, organ transplantation, long-term immuno-suppression, chemotherapy, and radiation therapy [9,10,11].

 Copyright©Ankara Hematoloji Onkoloji Derneği

Long-term immunosuppressant therapy has been shown to disrupt the immune surveillance of dysplastic cells. Systemic calcineurin inhibitors, one of the most commonly used immunosuppressants, can increase the risk of cSCC by blocking P53 signaling and nucleotide excision repair [12,13]. One of our patients after liver transplantation and another of our patients after kidney transplantation had used immunosuppressants for a long period (>6 months). The third patient was using both immunosuppressants and variconazole for GvHD that developed after allogeneic bone marrow transplantation.

Voriconazole, a triazole used for antifungal prophylaxis and treatment, has been associated with an increased risk of SCC after lung transplantation in adults and in HSCT recipients [14,15]. Voriconazole metabolites can induce both phototoxicity and photo-carcinogenesis by sensitizing keratino-cytes to ultraviolet A, inducing DNA fragility, and disrupting DNA repair [16,17}.

Radiotherapy is well-known to be carcino-genic, but its role in the pathogenesis of cSCC is not entirely clear. Despite the large amounts of data on sarcomas that develop in the background of scarring after radiotherapy [18] there are few reports on cSCCs developing after RT, especially in childhood. In our study, three (7%) of the patients had a history of radiotherapy in childhood. A multivariate analysis done in the large-sample study of the Childhood Cancer Survivor Study (CCSS) involving 13,132 patients revealed a six-fold risk increase in patients who had received radiotherapy in childhood versus those who did not [19].

Less is known about the occurrence of cSCC secondary to previous cancer treatment because data on the incidence of BCC or SCC were previously excluded from second malignancy analyses. The Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries reported a standard incidence rate of 4.7 (95% CI, 2.7 to 7.8) for non-melanoma cutaneous cancers in childhood cancer survivors compared to the general population [20]. To our knowledge, a history of chemotherapy has not previously been identified as an independent risk factor for cSCC. Given the significant overlap between patients that received radiotherapy and those that received chemotherapy in our study, we suggest that further studies are needed to confirm this finding.

Three (7%) of our patients had a predisposing genetic condition (Xeroderma pigmentosum in two patients and Gorlin's syndrome in one patient). While these three patients were diagnosed at a much earlier age than those with iatrogenic risk factors, a significant difference was found between them and the rest of the population in terms of both recurrence and reduced survival. Early diagnosis, careful sun protection and proper treatment of skin cancers can significantly reduce tumor burden and prolong life in these patients [21]. A fairly rare genetic disorder, xeroderma pigmentosum is characterized by photosensitivity, pigmentary changes in the skin, signs of premature aging, neoplasia, and abnormal DNA repair. It presents with defects in repairing DNA damage caused by UV rays and excessive sensitivity to UV rays, particularly to sunlight. Xeroderma pigmentosum should be borne in mind in the presence of easy sunburn, evidence of photosensitivity including lentigo, telangi-ectasia, ocular manifestations, or deafness [22]. Patients with familial cancer syndromes such as the nevoid BCC syndrome (Gorlin's syndrome) are also at risk of developing multiple BCC and SCC at an early age, as are patients with genetic defects in DNA repair mechanisms such as xeroderma pigmentosum [23,24,25].

Most of our patients were successfully treated with extensive surgical excision without metastases. Recurrence was seen in 41.9% of the patients in the follow-up period. Analysis of the factors associated with recurrence showed that the presence of histopatho-logically moderately-poorly differentiated SCC, prolonged use of immunosuppressants, and a history of radiotherapy and/or

 Copyright©Ankara Hematoloji Onkoloji Derneği

chemotherapy were associated with the development of recurrence. As mentioned above, factors other than differentiation are included as etiological factors in young adult cSCC. Therefore, patients should be regularly monitored since these factors are effective in both etiology and recurrence. Monitoring through follow-up visits is among the most effective interventions to be done to prevent recurrence.

The major limitation of our study is its retrospective nature and small number of patients. Given the rarity of cSCC in children and young adults, multicenter prospective studies are warranted to confirm and expand our findings. That most etiological and predisposing factors overlapped, and multiple risk factors were identified in patients may have influenced our results. Prospectively designed studies, in which tissue analyses of tumor suppressor genes and oncogene expression can be done with long-term follow-up, will shed light on both the pathogenesis and the treatment of the condition.

To conclude, although rarely fatal, cSCC is a major public health issue. In our study, we attempted to describe the predisposing conditions and iatrogenic exposures of young adult cSCC patients. The risk of developing cSCC is high in the presence of long-term use of immunosuppressants, chemoradiotherapy or genetic cutaneous cancer predisposition syndromes. Advising these patients to avoid exposure to UVR, such as to solar rays that may further increase the risk of cSCC, and early detection of the disease with regular follow-ups can prevent delays in diagnosis and minimize the burden of tumors.

REFERENCES

1. Stratigos AJ, Garbe C, Dessinioti C, et al. The European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 1. epidemiology, diagnostics and prevention. Eur J Cancer. 2020; 128: 60-82.

2. Holman JD, Dyer JA. Genodermatoses with malignant potential. Curr Opin Pediatr. 2007; 19: 446-454.

3. Xiang F, Lucas R, Hales S, Neale R. Incidence of nonmelanoma skin cancer in relation to ambient UV radiation in white populations, 1978-2012: empirical relationships. JAMA Dermatol. 2014; 150: 1063-1071.

4. Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol. 2014; 810: 120-140.

5. Rork JF, Margossian SP, Nambudiri VE, Huang JT. Nonmelanoma skin cancer in childhood after hematopoietic stem cell transplant: a report of 4 cases. J Pediatr Hematol Oncol. 2014; 36: 224-227.

6. Cowen EW, Nguyen JC, Miller DD, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatologist. 2010; 62: 31-37.

7. Unal S, Cetin M, Gumruk F. Basal cell carcinoma after treatment of childhood acute lymphoblastic leukemia and concise review of the literature. Pediatr Dermatol. 2015; 32: e82-e85.

8. Huang JT, Coughlin CC, Hawryluk EB, et al. Risk factors and outcomes of nonmelanoma skin cancer in children and young adults. J Pediatr. 2019; 211: 152-158.

9. Watt TC, Inskip PD, Stratton K, et al. Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2012; 104: 1240-1250.

10. Leisenring W, Friedman DL, Flowers ME, Schwartz JL, Deeg HJ. Nonmelanoma skin and mucosal cancers after hematopoietic cell transplantation. J Clin Oncol. 2006; 24: 1119-1126.

11. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003; 348: 1681-1691.

12. Muehleisen B, Jiang SB, Gladsjo JA, Gerber M, Hata T, Gallo RL. Distinct innate immune gene expression profiles in non-melanoma skin cancer immune-competent and immunosuppressed patients. PLoS One. 2012; 7: e40754.

13. Wheless L, Jacks S, Mooneyham Potter KA, Leach BC, Cook J. Skin cancer in organ transplant recipients: more than the immune system. J Am Acad Dermatol. 2014; 71: 359-365.

14. Feist A, Lee R, Osborne S, Lane J, Yung G. Increased incidence of cutaneous squamous cell carcinoma in

 Copyright©Ankara Hematoloji Onkoloji Derneği

lung transplant recipients taking long-term voriconazole. J Heart Lung Transplant. 2012; 31: 1177-1181.
15. Wojenski DJ, Bartoo GT, Merten JA, et al. Voriconazole exposure and the risk of cutaneous squamous cell carcinoma in allogenic hematopoietic stem cell transplant patients. Transpl Infection Dis. 2015; 17: 250-258.
16. Haylett AK, Felton S, Denning DW, Rhodes LE. Voriconazole-induced photosensitivity: photobiological assessment of a case series of 12 patients. Br J Dermatol. 2013; 168: 179-185.
17. Ona K, Oh DH. Voriconazole N-oxide and its ultraviolet B photoproduct sensitize keratinocytes to ultraviolet A. Br J Dermatol. 2015; 173: 751-759.
18. Kirova YM, Vilcoq JR, Asselain B, Sastre-Garau X, Fourquet A. Radiation-induced sarcomas after radiotherapy for breast carcinoma: a large-scale single-institution review. Cancer. 2005; 104: 856-863. 3
19. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2005; 23: 3733-3741.
20. Olsen JH, Garwicz S, Hertz H, et al. Second malignant neoplasms after cancer in childhood or adolescence. Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries. BMJ. 1993; 307: 1030-1036.
21. Moriwaki S, Kanda F, Hayashi M, Yamashita D, Sakai Y, Nishigori C, Xeroderma pigmentosum clinical practice guidelines revision committee. Xeroderma pigmentosum clinical practice guidelines. J Dermatol. 2017; 44: 1087-1096.
22. Black JO. Xeroderma Pigmentosum. Head Neck Pathol. 2016; 10: 139-144.
23. Gorlin RJ. Nevoid basal-cell carcinoma syndrome. Medicine (Baltimore). 1987; 66: 98-113.
24. Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. J Med Genet. 1993; 30: 460-464.
25. Cleaver JE, Crowley E. UV damage, DNA repair and skin carcinogenesis. Front Biosci. 2002; 7: d1024-d1043.

Corresponding author e-mail: zeynepgsevgen@hotmail.com

Orcid ID:
Zeynep Gülsüm Güç 0000-0001-8960-2208
Hasan Güç 0000-0002-1881-7487

Doi: 10.5505/aot.2023.61582

 Copyright©Ankara Hematoloji Onkoloji Derneği