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CASE REPORT

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Metastatic Laryngeal Squamous Cell Carcinoma Progressing with Subcutaneous Skin Metastasis Following Chemotherapy and Pembrolizumab Combination Treatment

Sait KİTAPLI[a], Ali ALKAN[a], Özgür TANRIVERDİ[a]

[a]Muğla Sıtkı Koçman University Faculty of Medicine, Division of Medical Oncology, Muğla, Türkiye

ABSTRACT The incidence of cutaneous metastasis of solid tumors is rare. Breast cancer is commonly associated with skin metastases. The frequency of cutaneous metastasis of lung and larynx cancers is high in men. The most common site of cutaneous metastases is the anterior thorax, followed by the abdomen, head and neck, scalp, and extremities. The prognosis of patients with cutaneous metastases is poor. The median life expectancy after skin metastasis development in most patients is 6 months. This study reported a 55-year-old patient diagnosed with metastasized laryngeal squamous cell carcinoma in which 90% of cells exhibited PD-L1 expression. After treatment with the combination of pembrolizumab and cisplatin-fluorouracil chemotherapy, the patient developed multiple subcutaneous skin metastases on the lower extremities and back after the fourth cycle. The review of previous scientific literature in the English language revealed only 16 subcutaneous skin metastasis cases. However, the development of skin metastases after immunotherapy has not been previously reported. Thus, visceral metastases may progress rapidly in patients with skin metastases, contributing to poor prognosis.

Keywords: Immunotherapy; laryngeal cancer; pembrolizumab; skin metastasis

Among head and neck cancers, laryngeal carcinoma accounts for the second highest incidence and mortality rates worldwide. The incidence of laryngeal cancer is high in individuals aged 55-65 years, men, and cigarette and alcohol consumers.[1] Squamous cell carcinoma (SCC) constitutes 95% of all laryngeal tumors.[2] In 65%-70% of laryngeal SCC cases, the tumor is mainly localized to the glottis, followed by the supraglottis and subglottis.[3] The general incidence of distant metastases in laryngeal cancers is approximately 8.5%, with the lung being the most common site of metastasis. The other common sites of metastasis are the bones and liver. The incidence of subcutaneous skin metastases, which are reported to develop frequently in the trunk, is rare.[4] Scientific literature review in the English language revealed only 16 previously reported cases of subcutaneous skin metastases of head and neck cancer (Table 1).

The incidence rate of skin metastasis from solid tumors is 0.7%-9%.[5] A meta-analysis in 2002 reported that the solid tumors in which cutaneous metastasis was most frequently observed were breast (24%), kidney (4%), ovary (3.8%), bladder (3.6%), lung (3.4%), colorectal (3.4%), and prostate (0.7%) cancers.[6] In a 2013 Brazilian study, the analysis of 209 patients with cutaneous metastases revealed that cutaneous metastasis commonly originated from breast and lung cancers in women (63.19%) and men (33.84%), respectively. The study also revealed that colon (10.41%) and lung cancers (4.16%) in women

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Correspondence: Sait KİTAPLI
Muğla Sıtkı Koçman University Faculty of Medicine, Division of Medical Oncology, Muğla, Türkiye
E-mail: kitaplisait@gmail.com

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TABLE 1: Previously reported cases of "larynx cancer" metastasizing to skin.

Author(s), year (reference)	Age	Gender	Histopathological differential diagnosis	Localization of skin metastasis	Clinical features, type of lesion
Veraldi et al., 1988	56	Male	Larynx SCC	On the forehead and left arm	Red-purple nodular lesion, palliative treatment
Horiuchi and Tagami, 1992	64	Male	Larynx SCC	Umbilical region	Subcutaneous nodular lesion, palliative CT
Bhandarkar et al., 1997	50	Male	Larynx SCC	Scalp, on the left clavicle and left foot	Cutaneous nodular lesion, lung metastasis
Bottoni et al., 2001	64	Male	Laryngeal Epidemoid Carsinoma	In the right supra and infraclavicular region	Inflammatory cutaneous metastasis
Şemsadini et al., 2003	58	Male	Larynx SCC	Grouped on right shoulder	Red purple nodular lesions, Palliative RT
Aydın et al., 2004	61	Male	Larynx SCC	Left hand in palmar region	Epidermal ulcerated lesion, Lung metastasis within two months
Krunic et al., 2006	49	Male	Supraglottic SCC	Infradiaphragmatic region	Painless subcutaneous nodule, erythematous lesion on the scalp, palliative RT
Ramin et al., 2009	75	Male	Larynx SCC	Left hip	Subcutaneous nodule
Kavgaci et al., 2010	-	-	Larynx SCC	Patella and right heel	Nodular lesion
Nikharika et al., 2015	65	Male	Hypopharyngeal SCC	Chest wall	Ulceroproliferative nodules
Kui-Rong Wang et al., 2016	54	Female	Atypical Laringeal carsinoid tumor	Abdominal region	Cutaneous and subcutaneous nodular lesions
Mandadi and Kudva, 2018	84	Male	Tongue-root SCC	Right hand 5th finger	Ulcero-proliferative lesion
Trehan et al., 2019	55	Male	Supraglottic SCC	Right hand and right forearm	Ulceroproliferative nodules, lung metastasis, palliative CT
Kumar et al., 2019	46	Male	Tongue-root SCC	Upper and lower extremities, fingertips and nails	Plaque nodular lesions, Lymph node, lung and bone metastases, Palliative CT
Araghi et al., 2020	58	Female	Larynx SCC	Localized on the right side of the face, neck and chin	Papulonodular lesions, CRT
Rafia Shahzad et al., 2024	45	Female	Hypopharyngeal SCC	Bilateral axillary region	Painful Subcutaneous lesions, Palliative treatment

SCC: Squamous cell carcinoma; CT: Chemotherapy; CRT: Chemoradiotherapy; RT: Radiotherapy.

and stomach (12.3%) and larynx cancers (7.69%) in men were the other most common solid tumors from which skin metastasis originated.[7]

This study reported a 55-year-old male patient with a rare metastatic laryngeal SCC, which progressed with multiple subcutaneous skin metastases in the lower extremities and back after treatment with the combination of pembrolizumab and first-line chemotherapy.

CASE REPORT

A 55-year-old male patient, who did not have a systemic chronic disease, complained of pain during swallowing. The mother and sister of the patient had a history of lung cancer, while an uncle died of larynx cancer. The patient had a smoking history (80 pack years) and consumed alcohol daily for 20 years. Examination revealed palpable cervical lymphadenopathies. Neck magnetic resonance imaging revealed the presence of transglottic larynx malignancy on the left and metastatic lymph nodes in D1-2-3-5. Biopsy analysis revealed an SCC diagnosis in May 2022. No pathological findings were observed on positron emission tomography-computed tomography (PET/CT) scan, except hypermetabolic metastatic lymph nodes [maximum standardized uptake value (SUV_{max})=3.7] in the cervical region. The size of the largest metastatic lymph node was 12 mm×15 mm. The metastasis was considered a locally advanced stage, and the patient was simultaneously treated with radiotherapy and cisplatin (40 mg/m^2) once a week.

An informed consent form was obtained from the patient.

Three months after chemoradiotherapy, a tracheostomy was performed due to complaints of difficulty in swallowing and shortness of breath. PET/CT scan revealed significant dimensional and metabolic regression in the primary hypermetabolic mass lesion in the larynx. A complete response was

noted in the lymph nodes of the left cervical region. However, a newly developed hypermetabolic cavitary nodule was detected in the lower lobe of the right lung. The right lung was subjected to a wedge resection, and the patient was diagnosed with laryngeal SCC metastasis.

A PET/CT scan was requested 2 months after the lung wedge resection of the patient, who could not receive treatment due to postoperative lung infection. New hypermetabolic metastatic lymph nodes were observed in the mediastinum (approximately 1.5 cm in the subcarinal region and approximately 1.1 cm in the lower right paratracheal region). The Eastern Cooperative Oncology Group (ECOG) performance status of the patient was 1. In the lung tissue, PD-L1 expression was detected in 70% of the cells. Hence, the patient was treated with the combination of pembrolizumab (200 mg/day), cisplatin (100 mg/m^2/day), and fluorouracil (1,000 mg/m^2 per day, 4-day infusion) once every 3 weeks as a first-line treatment. After the fourth cycle of chemotherapy, a PET/CT scan revealed an increase in the size of the primary tumor in the larynx and the presence of newly developed multiple metastatic lesions in the lung and vertebra. Thus, the disease was considered progressive (Figure 1). On examination, the patient had subcutaneous multiple nodular lesions on the back and lower extremities (Figure 2). In ultrasonography, an isoechoic nodular metastatic lesion containing calcific areas (16 mm×12 mm×27 mm) located subcutaneously in the extensor region of the left lower extremity was detected. The patient exhibited shortness of breath and cough and did not consent to undergo skin biopsy. The patient, whose ECOG performance

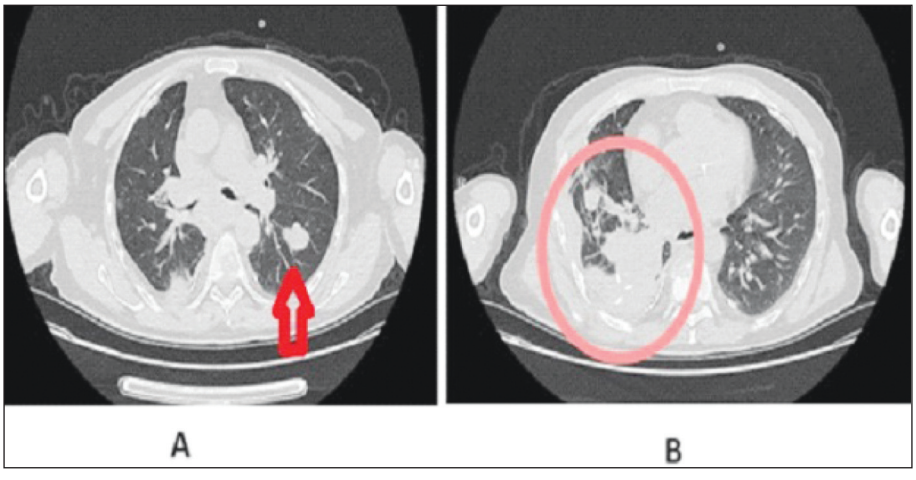

FIGURE 1: A) Metastatic lesions seen in both lungs; **B)** Nodular lesion with a size of 7 cm at the pleural base of the right lung and pleural effusion.

FIGURE 2: A) Subcutaneous nodular metastatic lesion on the extensor surface of the left lower extremity; **B)** Metastatic nodular lesions in the back region.

status was 1, was treated with cetuximab (400 mg/m^2 loading dose and then 250 mg/m^2 per week) in combination with cisplatin (75 mg/m^2/day) and docetaxel (75 mg/m^2/day) once every 3 weeks. When the patient visited for the third cycle, dimensional progression was observed in the subcutaneous multiple nodular lesions on the back and lower extremities. Palliative radiotherapy and supportive treatment were provided to the patient, who had developed hemoptysis along with increasing dyspnea. The patient, who was admitted to the intensive care unit due to respiratory failure on the sixth day of palliative radiotherapy, shortly passed away despite palliative treatments.

DISCUSSION

Pitman and Johnson reported that the frequency of skin metastasis in a cohort of 2,491 patients involving all head and neck cancer cases was 0.763% (n=19).[8] Yoskovitch et al. examined 798 patients with head and neck SCC and reported that the incidence rate of skin metastasis was 2.4% (n=19).[9] Laryngeal cancer frequently metastasizes to distant sites, such as the lung (66%), bone (22%), liver (10%), mediastinum, and bone marrow. However, the incidence of skin metastasis of laryngeal cancer was rare.

Distant skin metastases of laryngeal cancer may occur in laryngeal SCC, adenocarcinoma, and laryngeal atypical carcinoid tumors.[10] Skin metastases in laryngeal SCC can be in the form of inflammatory carcinoma and exhibit a zosteriform pattern with vesicles and bullae.[11] The case reported in this study had eruptive multiple papulonodular lesions.

The most common site of cutaneous metastases is the anterior thorax, followed by the abdomen, head and neck, and extremities. The site of cutaneous metastasis may indicate the primary tumor. Breast cancer most commonly metastasizes to the anterior part of the thorax.[5] The most common location of cutaneous metastases varies between head and neck carcinomas and laryngeal cancers (Table 1). Head and neck carcinoma tends to metastasize via direct dissemination. Thus, cutaneous metastatic lesions are usually close to this anatomical region.[12] Immune status may also influence the location of cutaneous metastases. The most sensitive areas are those with increased densities of regulatory T cells and decreased numbers of CD8 + T cells.[13]

Skin metastases are detected before the primary tumor in only one-third of cases. Meanwhile, most cases exhibit simultaneous visceral metastases.[5] Skin metastasis of the tumor indicates a poor prognosis.[14] The survival rate after diagnosis is low with 50% of patients dying within 6 months.[15] In this study, the disease progressed rapidly after the development of skin metastases.

Thus, skin metastasis is an indicator of poor prognosis and is considered a harbinger of distant organ metastasis. A case with presentations reported in this study, especially after immunotherapy, has not been previously reported. We presented this rare case to guide healthcare professionals in clinical practice.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özgür Tanrıverdi;* ***Design:*** *Sait Kitaplı, Özgür Tanrıverdi;* ***Control/Supervision:*** *Sait Kitaplı, Özgür Tanrıverdi;* ***Data Collection and/or Processing:*** *Sait Kitaplı, Ali Alkan;* ***Analysis and/or Interpretation:*** *Sait Kitaplı, Özgür Tanrıverdi;* ***Literature Review:*** *Sait Kitaplı, Ali Alkan, Özgür Tanrıverdi;* ***Writing the Article:*** *Sait Kitaplı, Özgür Tanrıverdi;* ***Critical Review:*** *Sait Kitaplı, Ali Alkan;* ***References and Fundings:*** *Sait Kitaplı, Özgür Tanrıverdi;* ***Materials:*** *Sait Kitaplı.*

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