# Atypical Site of Presentation of a Rare Type of SMARCA4-Positive Cutaneous Squamous Cell Carcinoma of the Skin: Case Report and Review of the Literature

**Ruchi Yadav, MD[1]** iD **, Shaun Din, MD[1], Harry Moussaris, MD[1],**
**Vivek Yadav, MD[2], Shakthi Raman, BSc[3], Anjula Gandhi, MD[1],**
**Boris Avezbakiyev, MD[1], and J. C. Wang, MD[1]** iD

## Abstract

Cutaneous squamous cell carcinoma (cSCC) comprises 20% of cases of nonmelanoma skin cancers in the United States. In total, 3% to 5% of squamous cell carcinoma (SCC) are metastatic at the time of presentation, associated with significant mortality due to a lack of standardized treatment options. In total, 95% of these tumors are amenable to the initial standard of treatment, which is surgical resection. However, a small percentage of them require systemic therapy as they are either locally advanced to regional lymph nodes or have distant metastasis. The common sites of presentation of cSCC are the scalp and the face with predictable spread to the intra-parotid, upper jugular, and perifacial lymph nodes. In our case report, however, our patient had a large lump lesion on the upper back, an unusual site of presentation of cSCC, with locally advanced metastasis to the left axillary lymph nodes. Subsequently, the tumor marker study revealed a positive SMARCA4 variant (the essential ATPase subunit of the Switch (SWI)/Sucrose Nonfermenting (SNF) chromatin-remodeling complex) that is even rarer in the context of cSCC. Furthermore, abnormalities in SWI/SNF chromatin-remodeling complex subunits have shown promising results as a target therapy for immune checkpoint inhibitor (ICI) therapy. We present an atypical presentation site of locally advanced rare variant SMARCA4-positive cSCC in a patient who received treatment with chemoradiation and systemic therapy with ICI after primary surgical resection. To date, only 2 cases of SMARCA4-positive cSCC were found in the literature with no details of the treatment received. Our case is unique in its atypical site of presentation as well as showing partial response to radiotherapy (RT) and systemic therapy with ICI.

## Keywords

cutaneous squamous cell carcinoma, SMARCA4 positive, immune checkpoint therapy, systemic chemotherapy

## Introduction

Cutaneous squamous cell carcinoma (cSCC) accounts for 20% of cutaneous malignancies and ranks as the second most common nonmelanoma skin cancer after basal cell carcinoma.[1] In total, 2% to 5% of cSCC have locally advanced tumors with metastases to regional lymph nodes.[2] The development and progression of cSCC involves mutations of genes, epigenetic modifications, viral infections, and tumor microenvironment factors that regulate the molecular etiopathogenesis of the tumor.[3] Pooled analysis studies have shown that genes responsible for chromatin remodeling and histone modifications demonstrated a higher burden of mutations in metastatic tumors as compared to nonmetastatic tumors of the skin.[4] Several significant genes and their mutations play an important role in the

genesis of head and neck squamous cell carcinoma (SCC) including TP53, CDKN2A, HRAS, PTEN, and PIK3CA.[5] SMARCA4 subgroup of genes, belonging to the SWI1/SNF1 family of chromatin repair, has recently gained attention as a

[1]Brookdale University Hospital Medical Center, Brooklyn, NY, USA
[2]State University of New York Downstate Health Sciences University, Brooklyn, NY, USA
[3]Medical University of Lublin, Poland

**Corresponding Author:**
Ruchi Yadav, 151-15, 82nd street, Howard Beach, Queens, Brooklyn, NY 11414, USA.
Email: drruchi2776@gmail.com

**Figure 1.** On examination, around 10 cm × 8 cm mass was noted on the left upper back, soft in consistency, mildly tender with central ulceration and serosanguinous fluid, non–foul-smelling oozing out of it.



**Figure 2.** CT thoracic spine axial view showing 9.3 cm lesion on upper back marked by the red arrow.

substantial oncogenic molecule that can be potentially targeted in cancer therapies.[6] SMARCA4-deficient undifferentiated malignant neoplasms (SD-UMN) are a known entity of aggressive type of lung carcinoma;[7] however, SMARCA4-positive genomic variant in cSCC is not well known and is considered as a very rare presentation. To date, only 2 cases of primary cutaneous SD-UMN have been reported.[8] With regard to SMARCA4-positive cSCC, we were able to find 2 case reports, namely, a case involving a 74-year-old Caucasian male with cSCC of the head and neck who was treated with pembrolizumab[9] and the other was a research article based on genomic variants of cSCC showing 1 sample positive for SMARCA4.[10]

## Case Report

Our patient is a 50-year-old male who presented with a mass on the left upper back that was increasing in size associated with fluid oozing and ulceration. The mass grew to its present size of approximately 10 cm × 8 cm more than 2 to 3 months. He had no significant past medical history or family history of cancer. He worked as a porter in a building, and the occupation did not involve exposure to sun or outdoor activities. He denied any s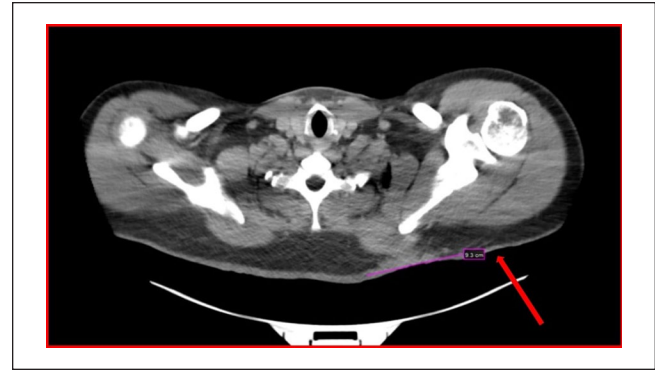moking or use of substances. On examination, around 10 cm × 8 cm mass was noted on the left upper back with central ulceration and serosanguinous fluid, non–foul-smelling oozing out of it (Figure 1). The mass was mildly tender, restrictive mobility, and soft in consistency. Computed tomography thoracic spine was done and showed 7.5 cm × 9 cm × 4.2 cm heterogeneous well-defined superficial soft tissue mass in the left upper back with infiltration to the adipose tissue (Figure 2). He underwent an incisional biopsy of the mass on the back, and the tissue was sent for pathology. Per operative findings approximately 10 cm × 10 cm ulcerated mass on the back located on the left scapula area. Preliminary pathology reported SCC of skin. The patient was planned for wide local excision of the mass (Figure 3) that was done with a pathology report (Figures 4 and 5) showing invasive high-grade SCC, poorly differentiated with marked cytological atypia and foci of tumor necrosis. The invasive margin reached 1 mm of the deep inked margins. Ki-67 was 60% on Immunohistochemical stain. Additional testing for human papillomavirus (HPV) RNA (6/11, 16/18, 31/33) was negative. The patient had left axillary lymphadenopathy palpable clinically with approximately 3 lymph nodes that showed associated perinodal soft tissue invasion seen in 1 of the 2 lymph nodes with soft tissue inflammation after resection.

Positive genomic variants noted on the tumor biopsy block using next-generation sequencing (NGS) were SMARCA4 T910M, CDKN2A Y129fs, ERBB2 V777L, and TP53 C242fs. Positron emission tomography-computed tomography (PET-CT) scan done—hypermetabolic skin thickening in the left upper back (Figure 6A and B), hypermetabolic subcutaneous nodule/lymph node in the left posterolateral upper back with hypermetabolic left axillary lymphadenopathy noted (Figure 7), which is most consistent with metastatic nodal disease. No other distant metastasis was noted.

The patient was admitted again for a planned procedure of split-thickness skin graft for the open wound on the left upper back. After healing of the wound, he was started on

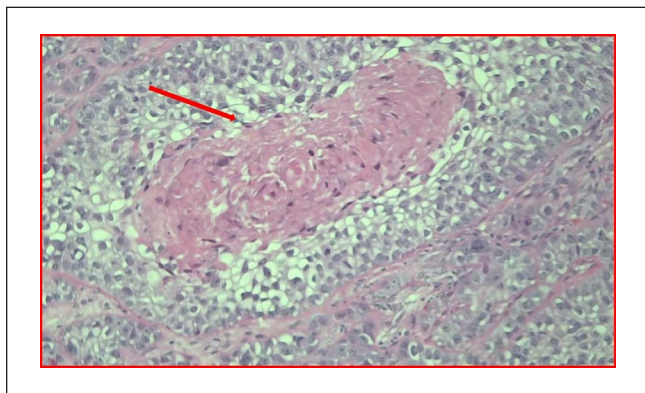Figure 3. Wide local excision of the tumor mass on the upper back.



**Figure 4.** Showing 40× magnification area with dense pink cytoplasmic keratinization marked by the red arrow and H&E staining showing cells suggestive of features of SCC.



**Figure 5.** Showing high power field (HPF) 100× magnification of cells with features of invasive, high-grade, poorly differentiated with marked cytological atypia shown by the red arrow and foci of tumor necrosis of SCC.

radiotherapy (RT) along with a radiation-sensitizing dose of cisplatin that continued for 8 weeks. He was regularly followed up in the clinic. During the last week of his treatment, he developed an acute onset of dysphagia with the inability to tolerate both solid and liquid food associated with severe retching, gag reflex, and vomiting which were likely adverse effects of chemo-RT. During his hospital stay, CT ches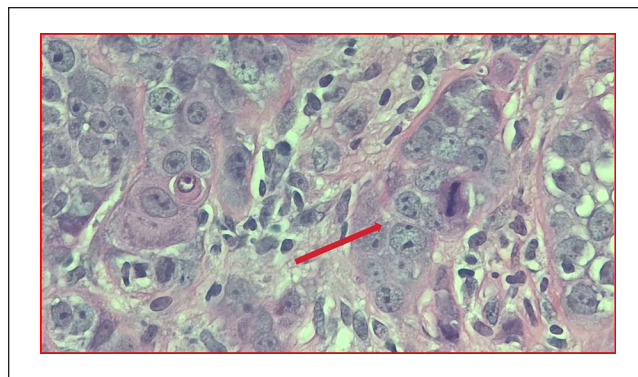t/abdomen/pelvis without contrast showed pleural-based pulmonary metastases that were questionable with scattered hypodense liver lesions the largest in the right hepatic lobe measuring 4 cm. Liver biopsy was done, and pathology was consistent with liver hemangioma and not metastasis. The pleural-based pulmonary findings were reviewed by the radiologist, and the decision was taken to observe them over a while with one of the differentials being RT-induced changes. Given the high risk of local progression of the disease, the patient started on systemic therapy with pembrolizumab.

After completion of RT and receiving 3 cycles of immune checkpoint inhibitor (ICI), the patient underwent his first surveillance PET scan (approximately 9 months after the diagnosis), which showed interval resolution of the hypermetabolic activity in the left axillary lymph nodes; however, a new hypermetabolic 2.2 cm nodule appeared in the skin and subcutaneous tissues inferior to the mildly hypermetabolic soft tissue changes in the left upper back with the standard uptake values (SUV) ranging from 5.8 to 11.2 (Figure 8). On examination, the site of the lesion appeared well-healed with no clinical palpable nodule or lymph node in the axilla (Figure 9). To summarize the response of the tumor after receiving appropriate chemo-RT treatment, the patient had resolution of the original lesion but developed new hypermetabolic skin findings adjacent to the original site pointing toward a locally progressive process.

The case was discussed in the tumor board after the clinical course showed local disease progression after 9 months of treatment and a decision was taken by the multidisciplinary team to observe and switch systemic therapy from ICI to carboplatin, paclitaxel, and cetuximab (monoclonal antibody for EGFR) based on *The National Comprehensive Cancer Network (NCCN)* Guidelines. The patient is currently under close surveillance of oncology, radiation oncology, and surgery teams receiving systemic therapy and under watchful monitoring with regular PET scans.

**Figure 6.** (A) Axial view PET scan showing heterogeneous hypermetabolic activity in skin thickening in the left upper back, marked by the red arrow, approximately 9.3 cm in length. The standard uptake values of this activity range from 3.5 to 4.4. (B) Sagittal view PET scan showing heterogeneous hypermetabolic activity in skin thickening in the left upper back, marked by the red arrow, approximately 9.3 cm in length. The standard uptake values of this activity range from 3.5 to 4.4.
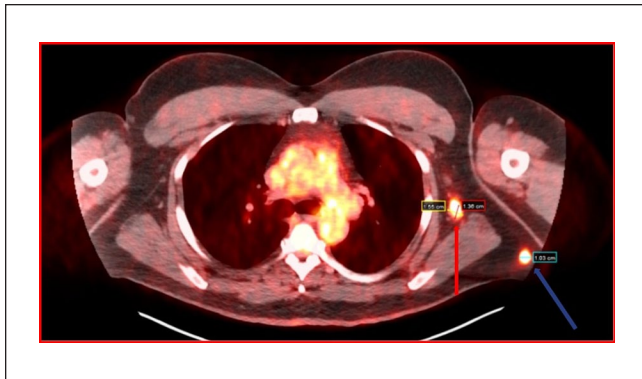


**Figure 7.** Positron emission tomography (PET) scan image showing left axillary lymphadenopathy as marked by blue and red arrows with largest one approximately 1 cm that were resected and showed associated perinodal soft tissue invasion seen in 1 of the 2 lymph nodes.

## Discussion

SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4) plays an important role in organ development by regulating gene expression, DNA repair, and chromatin accessibility.[11] The SMARCA4 protein acts like a catalytic subunit of the SWI/SNF complex with ATPase activity.[12] There are several SMARCA4 variants identified in human malignancies as evidenced by a recent study done by Fernando et al.[13] Alteration of SMARCA4, leading to mutation in chromatin-remodeling SWI/SNF complex genes and tumor immunity, is found in 3% to 7% of all malignant neoplasms.[14] In medical literature, SMARCA4-deficient undifferentiated tumor

(SMARCA4-dUT) of the lung/thorax, small cell carcinoma of the ovary with hypercalcemia type (SCCOHT), and SMARCA4-deficient non–small-cell lung carcinoma (SMARCA4-dNSCLC) are well-known entities.[15] However, in head and neck squamous cell cancers (HNSCC), common genes implicated in the malignancy are TP53, CDKN2A, PTEN, PIK3CA, HRAS, NOTCH1, IRF6, and TP63, whereas SMARCA4 dysregulation is found in only small subset of the cases.[5]

There are approximately 1.8 million cases of cSCC annually in the United States.[16] The clinical presentation of cSCC can vary from low-risk SCC in situ to high-risk locally advanced or metastatic cancers with the regional lymph node being the most common site.[17] In the United States, there are 2 staging systems used for cSCC that help predict the risk of metastasis, namely those by Brigham and Women's Hospital (BWH) and the American Joint Committee on Cancer (AJCC) eighth edition.[18,19] The NCCN guidelines, proposed in 2022, categorically divide cSCC into high-risk and very high-risk cSCC based on the presence of risk factors for local recurrence, metastasis, or death to aid in the direction of patient management.[16,20]

There are multifactorial mechanisms involved in the etiopathogenesis of cSCC including environmental, genetic, and immunological factors. Major predisposing factors include ultraviolet rays, cumulative sun exposure, psoralen and ultraviolet A (PUVA) treatment for skin diseases, HPV subtypes infection, smoking, immunosuppression, and being organ transplantation recipients.[21-23] The risk of metastasis in primary cSCC is usually assessed by features including location (lip, ear), immunosuppression, tumor thickness, poor differentiation, previous scar tissue, perineural infiltration, and
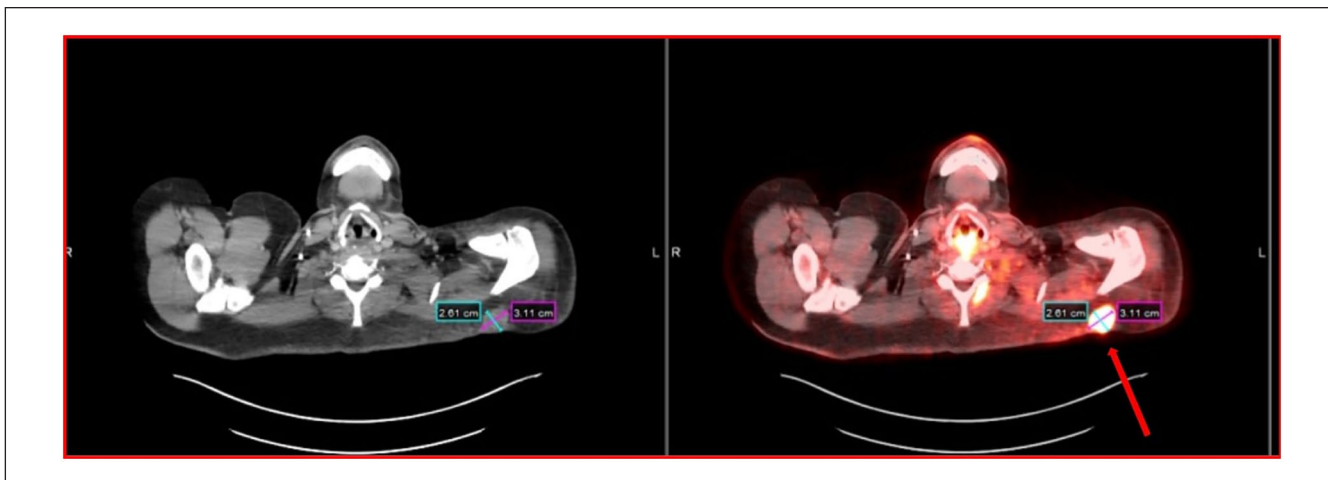
**Figure 8.** Surveillance PET scan done 1 year later showed a new hypermetabolic 2.2 cm nodule (marked by the red arrow) in the skin and subcutaneous tissues inferior to the mildly hypermetabolic soft tissue changes in the left upper back with the standard uptake values (SUV) ranging from 5.8 to 11.2.



**Figure 9.** After 1 year of treatment on examination, the site of the lesion appeared well-healed with no clinical palpable nodule.

lymphovascular invasion (LVI).[24] Invasive cSCC is usually seen in sun-exposed areas with 55% developing in the head and neck area and 18% on the dorsum of hand and forearms.[25] The upper back is an extremely rare site for cSCC as it only accounts for 4% of the reported incidence.[25] Poorly differentiated cSCC presents as a soft, ulcerated, rapidly growing lesion with distant metastasis as seen in 27% of the cases.[26] In our case, the patient developed a rapidly enlarging mass more than 2 to 3 months on the upper back with ulceration with metastasis in 2 out of 14 lymph nodes that were resected. At the time of presentation to the clinic, the patient had stage IV invasive cSCC (T3N2bM0) based on the AJCC Staging for cSCC (eighth edition, 2017) (Tables 1 and 2).[19] The characteristics of a high-risk lesion are clinical and notable pathological variables include size, location, poorly defined borders, rapidly growing tumor, perineural invasion (PNI), LVI, poorly differentiated pathology, modified Breslow thickness >4 mm, previous history of RT, and neurological symptoms.[21]

Histologically invasive cSCC is recognized by atypical keratinocytes with hyperchromatic, pleomorphic nuclei with mitoses, in addition to locally destructive growth with an increased risk of metastasis. The Broder staging is a predictor of prognosis that includes grading of the lesion: grade I includes tumors composed of <25% undifferentiated cells, grade II lesions with <50% undifferentiated cells, grade III lesions with <75% undifferentiated cells, and grade IV lesions with >75% undifferentiated cells.[27] Surgical resection is the primary modality of treatment for the majority of cSCC however 5% metastasize to nearby lymph nodes leading to a 3-year disease-free survival rate of 56% and a 5-year survival rate of 25% to 35%.[28-30]

To understand the molecular mechanism of etiopathogenesis of cSCC, we need to gain knowledge about the several genomic variants implicated in cSCC. SMARCA4 gene is located on chromosome 19p and encodes BRG1 (Brahma-related gene 1) protein, forming part of SWI/SNF chromatin-remodeling complex.[31] Approximately 20% of malignancies are found to have abnormalities in one of the genes encoding

**Table 1.** TNM definitions for cutaneous carcinoma of the head and neck based on American Joint Committee on Cancer (AJCC) Staging for cSCC (eighth edition, 2017).

| T | Primary tumor |
| --- | --- |
| Tx | Tumor cannot be assessed |
| Tis | Carcinoma in situ |
| T1 | Tumor smaller ≤2 cm in largest dimension |
| T2 | Tumor >2 cm, but ≤4 cm in largest dimension |
| T3 | Tumor >4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion |
| T4 | Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion |
| T4a | Tumor with gross cortical bone/marrow invasion |
| T4b | Tumor with skull base invasion and/or skull base foramen involvement |
| **cN (Clinical)** | **Regional lymph nodes (LN)** |
| Nx | Regional LN cannot be assessed |
| N0 | No regional LN metastasis |
| N1 | Metastasis in a single ipsilateral LN, ≤3 cm in largest dimension and extra nodal extension (ENE)(−) |
| N2a | Metastasis in a single ipsilateral LN >3 cm but <6 cm in largest dimension and ENE(−) |
| N2b | Metastases in multiple ipsilateral LN, <6 cm in largest dimension and ENE(−) |
| N2c | Metastases in bilateral or contralateral LN, <6 cm in largest dimension and ENE(−) |
| N3a | Metastasis in a lymph node >6 cm in largest dimension and ENE(−) |
| N3b | Metastasis in any node(s) and ENE (+) |
| **M** | **Distant metastasis** |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

Abbreviations: LN, lymph node; ENE, extra nodal extension.

**Table 2.** Showing AJCC staging of cSCC (eighth edition, 2017).

| Stages | T | N | M |
| --- | --- | --- | --- |
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T3 | N0 | M0 |
| | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage IV | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N2 | M0 |
| | Any T | N3 | M0 |
| | T4 | Any N | M0 |
| | Any T | Any N | M1 |

for the subunits, which thus confers promising results for the gene mutations in terms of acting as a marker for ICI responsiveness.[14] There were 2 kinds of mutations observed in the SMARCA4 category namely loss of function class 1 mutations and missense class 2 mutations.[32] A comprehensive analysis of genomic mutation in cSCC revealed several functionally significant somatic alterations belonging to cancer signaling pathways mainly the RAS/RTK/PI3K pathway, cell cycle pathway, squamous cell differentiation pathway, and chromatin-remodeling genes.[33] Yilmaz et al[4] analyzed exome and targeted sequencing studies to identify potential driver mutations on cSCC; most were found to have mutations of tumor suppressor tumor protein p53 (*TP53*), NOTCH pathway genes, CDKN2A, KMT2D, and KAT6A. Among the DNA repair genes, however, SMARCA4 mutation contributed around 33%. Frequent somatic alteration of the SMARCA4 gene, known for tumor suppressor function, was estimated to be approximately 5% in the HPV-negative viral subgroup.[5] Treatment modalities for patients with metastatic cSCCs are lacking and have been limited by a lack of knowledge of the genomic alterations that drive metastatic cSCCs. In addition, there are no validated molecular biomarkers predictive of disease behavior or treatment response. Currently, numerous trials are underway to investigate a combination of targeted therapies and immunotherapies in conjunction with chemotherapy or RT in an adjuvant and neoadjuvant setting.[34] After searching the literature, we found only couple of case reports of SMARCA4-positive cSCC including study done by Yvonne Li et al[10] on the genomic analysis of metastatic cSCC identifying 1 sample with SMARCA4 mutation; however, no details of the case were given in the article.

Surgical excision with a 4 to 6 mm margin of uninvolved skin around the tumor is the standard care of treatment for low-risk cSCC, with the American Academy of Dermatology (AAD) recommending excision to the depth of the

subcutaneous adipose tissue.[35] However, there are limited data available for defining peripheral and deep margins for excision of high-risk tumors with standard excision as our case belonged to that category. A linear repair, skin graft, or healing by secondary intention is considered a surgical treatment modality for high-risk cSCC.[36]

The role of adjuvant RT coupled with systemic therapy has been well-studied for high-risk cSCC.[37] The AAD recommends adjuvant RT for cSCC with concerning high-risk features including PNI and regional or distant metastasis after surgical excision. However, as per guidelines, there is no high-level evidence to support this treatment approach.[35] Similarly, adjuvant chemotherapy with platinum-based agents (cisplatin and carboplatin) and an anti-metabolite with 5-FU have been used for locally advanced/metastatic tumors but need more future prospective data to support the regimen.[38] The use of systemic chemotherapy has been able to achieve partial response in 34% to 44% of the cases with median progression-free survival (PFS) and overall survival (OS) of about 5 and 11 months, respectively, as evident in nonrandomized trials.[39] Targeted therapy has been used for advanced cSCC expressing epidermal growth factor receptor (EGFR) which is inversely correlated with clinical outcome and the degree of expression does not correlate with EGFR inhibitor's efficacy.[40] Cetuximab (monoclonal antibody for EGFR) obtained an objective response of 28% with a mean OS of 8.1 months in a phase II study in which it was used as a first-line monotherapy in patients with unresectable SCC of the skin.[41]

There has been a strong link between the immune system, innate immunosurveillance, mutational burden, and pathogenesis of cSCC. Studies have proven that immunodeficient states along with several mechanisms emphasizing the role of immune-tolerant microenvironment promote a higher risk of developing cSCC.[42,43] Inflammatory cytokines, including IL-6, IL-10, IL-2, and TGF-beta, promote infiltration of Treg cells and myeloid-derived suppressor cells (MDSCs) that actively suppress CD4/CD8 T lymphocytes thus creating a tumor microenvironment that stimulates proliferation of tumor cells.[44] The expression of an immune checkpoint molecule such as programmed-death ligand 1 (PD-L1) is upregulated in cSCC showing a positive correlation between PD-L1 expression and risk of metastasis.[45] A study conducted by Hanna et al[34] evaluated the tumor mutational landscape in squamous cell carcinoma of the head and neck (SCCHN) based on anti-PD-1/L1 response and found that nonexclusive somatic alterations in *NOTCH1, TP53, KMT2D*, and *SMARCA4* were the most commonly reported mutations among the 12 sequenced responders out of 81 cohort of patients. Currently, cemiplimab and pembrolizumab, monoclonal antibodies that bind to PD-1 and block the interaction with its ligands PD-L1/L2 have been studied and recommended for locoregional advanced or metastatic cSCC.[46]

A phase 1 multicohort study[47] ($n = 26$ patients) and phase II EMPOWER-CSCC study[48,49] ($n = 193$ patients) investigated and demonstrated the safety and efficacy of cemiplimab in cSCC. In total, 33.7% of patients had prior systemic treatment while 90.2% had prior surgery and 67.9% had received prior RT.[50] Independent central review showed that the response rate was 50% with a duration of response that exceeded 6 months in 7 of the 13 responding patients.[47] In the phase II study, 3 groups were present, namely group 1 (metastatic cSCC), group 2 (locally advanced cSCC) received 3 mg/kg once every 2 weeks, and group 3 (metastatic cSCC) received 350 mg once every 3 weeks. An objective response was noted in 49.2%, 43.6%, and 41.1% of patients in groups 1, 2, and 3, respectively, with a median response time of 1.9 months in groups 1 and 2 and 2.1 months in group 3.[48] Median OS and PFS were not reached by any treatment group.

In addition, KEYNOTE 629 ($n = 105$ patients) and CARSKIN ($n = 57$ patients), both phase II multicentric trials, investigated the use of pembrolizumab in cSCC.[51] In both groups, patients had received prior therapies either systemic or RT and showed the objective response rate of 34% with 69% experiencing durable responses longer than 6 months. On follow-up for approximately 10 months, the 1-year OS was 60% and the median PFS was 7 months. In the future, innovative regimens combining RT with immunotherapy are being proposed and studied under the UNSCARRed trial, which acts to combine avelumab (PD-L1 antibody) with radical RT[52] (clinicaltrials.gov: NCT03737721).

Our patient underwent wide surgical excision of the mass along with lymph node dissection of the left axillary region. He received concomitant chemoradiation with cisplatin and RT for 8 weeks. Given his tumor being high risk (LVI, bulky, positive lymph nodes), he was started on pembrolizumab after chemo-RT. He demonstrated partial response by resolution of hypermetabolic lymph nodes in the left axilla and the primary site at the upper back; however, a new lesion appeared adjacent to the primary site. Nevertheless, the time gap of progression of the disease in our case was approximately 1 year which by itself is a rare finding keeping in mind the highly aggressive nature of SMARCA4-positive variant in any tumor with median survival being approximately 6 to 8 months. Currently, we are awaiting the response of the tumor to the changed treatment plan from ICI to chemotherapy (carboplatin, paclitaxel, and cetuximab) based on NCCN guidelines.

## Conclusion

Therapies for patients with metastatic cSCCs are lacking and have been limited by a dearth of knowledge of the genomic alterations that drive metastatic cSCCs. In addition, there are no validated molecular biomarkers predictive of disease behavior or treatment response. SMARCA4 is involved in developmental processes, transcriptional regulation, DNA

repair, cell cycle control, and cancer genesis. Our case study encompasses the prognostic landscape of SMARCA4 expression and mutation across cancers as well as its role in regulating tumor microenvironment. This article elucidates the consequential need to conduct high-level research to identify several drug targets/ligands that can help with the development of new systemic therapies, including immunotherapy resulting in improved OS and clinical outcome of cSCC.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

## ORCID iDs

Ruchi Yadav https://orcid.org/0000-0002-8207-2424

J. C. Wang https://orcid.org/0000-0002-9623-6645

## References

1. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol*. 2018;78(2):237-247. doi:10.1016/j.jaad.2017.08.059
2. Vasan K, Low TH, Gupta R, et al. Lymph node ratio as a prognostic factor in metastatic cutaneous head and neck squamous cell carcinoma. *Head Neck*. 2018;40(5):993-999. doi:10.1002/hed.25066
3. Nissinen L, Farshchian M, Riihilä P, Kähäri VM. New perspectives on role of tumor microenvironment in progression of cutaneous squamous cell carcinoma. *Cell Tissue Res*. 2016;365(3):691-702. doi:10.1007/s00441-016-2457-z
4. Yilmaz AS, Ozer HG, Gillespie JL, et al. Differential mutation frequencies in metastatic cutaneous squamous cell carcinomas versus primary tumors. *Cancer*. 2017;123(7):1184-1193. doi:10.1002/cncr.30459
5. Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. *Science*. 2011;333(6046):1157-1160. doi:10.1126/science.1208130
6. Chetty R, Serra S. SMARCA family of genes. *J Clin Pathol*. 2020;73(5):257-260. doi:10.1136/jclinpath-2020-206451
7. Yadav R, Sun L, Salyana M, Eric M, Gotlieb V, Wang JC. SMARCA4-Deficient undifferentiated tumor of lung mass-a rare tumor with the rarer occurrence of brain metastasis: a case report and review of the literature. *J Investig Med High Impact Case Rep*. 2022;10:23247096221074864. doi:10.1177/23247096221074864
8. Russell-Goldman E, MacConaill L, Hanna J. Primary cutaneous SMARCA4-deficient undifferentiated malignant neoplasm: first two cases with clinicopathologic and molecular comparison to eight visceral counterparts. *Mod Pathol*. 2022;35(12):1821-1828. doi:10.1038/s41379-022-01152-1
9. Ravulapati S, Leung C, Poddar N, Tu Y. Immunotherapy in squamous cell skin carcinoma: a game changer? *Am J Med*. 2017;130(5):e207-e208. doi:10.1016/j.amjmed.2016.12.020
10. Li YY, Hanna GJ, Laga AC, et al. Genomic analysis of metastatic cutaneous squamous cell carcinoma. *Clin Cancer Res*. 2015;21(6):1447-1456. doi:10.1158/1078-0432.CCR-14-1773
11. Li W, Xiong Y, Shang C, et al. Brg1 governs distinct pathways to direct multiple aspects of mammalian neural crest cell development. *Proc Natl Acad Sci U S A*. 2013;110(5):1738-1743. doi:10.1073/pnas.1218072110
12. Xiong Y, Li W, Shang C, et al. Brg1 governs a positive feedback circuit in the hair follicle for tissue regeneration and repair. *Dev Cell*. 2013;25(2):169-181. doi:10.1016/j.devcel.2013.03.015
13. Fernando TM, Piskol R, Bainer R, et al. Functional characterization of SMARCA4 variants identified by targeted exome-sequencing of 131,668 cancer patients. *Nat Commun*. 2020;11(1):5551. doi:10.1038/s41467-020-19402-8
14. Hodges C, Kirkland JG, Crabtree GR. The many roles of BAF (mSWI/SNF) and PBAF complexes in cancer. *Cold Spring Harb Perspect Med*. 2016;6(8):a026930. doi:10.1101/cshperspect.a026930
15. Pan M, Jiang C, Zhang Z, et al. Sex- and co-mutation-dependent prognosis in patients with SMARCA4-mutated malignancies. *Cancers*. 2023;15(10):2665. doi:10.3390/cancers15102665
16. Burns C, Kubicki S, Nguyen QB, et al. Advances in cutaneous squamous cell carcinoma management. *Cancers*. 2022;14(15):3653. doi:10.3390/cancers14153653
17. Tokez S, Wakkee M, Kan W, et al. Cumulative incidence and disease-specific survival of metastatic cutaneous squamous cell carcinoma: a nationwide cancer registry study. *J Am Acad Dermatol*. 2022;86(2):331-338. doi:10.1016/j.jaad.2021.09.067
18. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol*. 2013;149(4):402-410. doi:10.1001/jamadermatol.2013.2456
19. Breuninger H, Brantsch K, Eigentler T, Häfner HM. Comparison and evaluation of the current staging of cutaneous carcinomas. *J Dtsch Dermatol Ges*. 2012;10(8):579-586. doi:10.1111/j.1610-0387.2012.07896.x
20. Chu MB, Slutsky JB, Dhandha MM, et al. Evaluation of the definitions of "high-risk" cutaneous squamous cell carcinoma using the American Joint Committee on Cancer staging criteria and national comprehensive cancer network guidelines. *J Skin Cancer*. 2014;2014:154340. doi:10.1155/2014/154340
21. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 1. Epidemiology, diagnostics and prevention. *Eur J Cancer*. 2020;128:60-82. doi:10.1016/j.ejca.2020.01.007

22. Chahoud J, Semaan A, Chen Y, et al. Association between β-genus human papillomavirus and cutaneous squamous cell carcinoma in immunocompetent individuals-a meta-analysis. *JAMA Dermatol*. 2016;152(12):1354-1364. doi:10.1001/jamadermatol.2015.4530

23. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. *JAMA Dermatol*. 2017;153(3):296-303. doi:10.1001/jamadermatol.2016.4920

24. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol*. 2013;68(6):957-966. doi:10.1016/j.jaad.2012.11.037

25. Kallini JR, Hamed N, Khachemoune A. Squamous cell carcinoma of the skin: epidemiology, classification, management, and novel trends. *Int J Dermatol*. 2015;54(2):130-140. doi:10.1111/ijd.12553

26. Fania L, Didona D, Di Pietro FR, et al. Cutaneous squamous cell carcinoma: from pathophysiology to novel therapeutic approaches. *Biomedicines*. 2021;9(2):171. doi:10.3390/biomedicines9020171

27. Paolino G, Donati M, Didona D, et al. Histology of non-melanoma skin cancers: an update. *Biomedicines*. 2017;5(4):71. doi:10.3390/biomedicines5040071

28. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol*. 1992;26(6):976-990. doi:10.1016/0190-9622(92)70144-5

29. Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. *Aust N Z J Surg*. 1992;62(9):697-701. doi:10.1111/j.1445-2197.1992.tb07065.x

30. Kraus DH, Carew JF, Harrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*. 1998;124(5):582-587. doi:10.1001/archotol.124.5.582

31. Krishnamurthy N, Kato S, Lippman S, et al. Chromatin remodeling (SWI/SNF) complexes, cancer, and response to immunotherapy. *J Immunother Cancer*. 2022;10(9):e004669. doi:10.1136/jitc-2022-004669

32. Tang L, Nogales E, Ciferri C. Structure and function of SWI/SNF chromatin remodeling complexes and mechanistic implications for transcription. *Prog Biophys Mol Biol*. 2010;102(2-3):122-128. doi:10.1016/j.pbiomolbio.2010.05.001

33. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489(7417):519-525. doi:10.1038/nature11404

34. Hanna GJ, Lizotte P, Cavanaugh M, et al. Frameshift events predict anti–PD-1/L1 response in head and neck cancer. *JCI Insight*. 2018;3(4):e98811. doi:10.1172/jci.insight.98811

35. Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78(3):560-578. doi:10.1016/j.jaad.2017.10.007

36. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. *JAMA Dermatol*. 2016;152(4):419-428. doi:10.1001/jamadermatol.2015.4994

37. Newman JG, Hall MA, Kurley SJ, et al. Adjuvant therapy for high-risk cutaneous squamous cell carcinoma: 10-year review. *Head Neck*. 2021;43(9):2822-2843. Accessed August 7, 2024. https://onlinelibrary.wiley.com/doi/full/10.1002/hed.26767

38. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. *Laryngoscope*. 2005;115(5):870-875. Accessed August 7, 2024. https://onlinelibrary.wiley.com/doi/abs/10.1097/01.MLG.0000158349.64337.ED

39. Jarkowski A 3rd, Hare R, Loud P, et al. Systemic therapy in advanced Cutaneous Squamous Cell Carcinoma (CSCC): the Roswell Park experience and a review of the literature. *Am J Clin Oncol*. 2016;39(6):545-548. Accessed August 7, 2024. https://journals.lww.com/amjclinicaloncology/abstract/2016/12000/systemic_therapy_in_advanced_cutaneous_squamous.2.aspx

40. Foote MC, McGrath M, Guminski A, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. *Ann Oncol*. 2014;25(10):2047-2052. doi:10.1093/annonc/mdu368

41. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011;29(25):3419-3426. doi:10.1200/JCO.2010.34.1735

42. Büttner R, Longshore JW, López-Ríos F, et al. Implementing TMB measurement in clinical practice: considerations on assay requirements. *ESMO Open*. 2019;4(1):e000442. doi:10.1136/esmoopen-2018-000442

43. Lai C, August S, Albibas A, et al. OX40+ regulatory T cells in cutaneous squamous cell carcinoma suppress effector T-Cell responses and associate with metastatic potential. *Clin Cancer Res*. 2016;22(16):4236-4248. doi:10.1158/1078-0432.CCR-15-2614

44. Bluth MJ, Zaba LC, Moussai D, et al. Myeloid dendritic cells from human cutaneous squamous cell carcinoma are poor stimulators of T-cell proliferation. *J Invest Dermatol*. 2009;129(10):2451-2462. doi:10.1038/jid.2009.96

45. Slater NA, Googe PB. PD-L1 expression in cutaneous squamous cell carcinoma correlates with risk of metastasis. *J Cutan Pathol*. 2016;43(8):663-670. doi:10.1111/cup.12728

46. Alberti A, Bossi P. Immunotherapy for cutaneous squamous cell carcinoma: results and perspectives. *Front Oncol*. 2022;11:727027. Accessed October 22, 2023. https://www.frontiersin.org/articles/10.3389/fonc.2021.727027

47. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379(4):341-351. doi:10.1056/NEJMoa1805131

48. Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. *J Immunother Cancer*. 2020;8(1):e000775. doi:10.1136/jitc-2020-000775

49. Migden MR, Khushalani NI, Chang ALS, et al. Primary analysis of phase 2 results of cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with locally advanced cutaneous

squamous cell carcinoma (laCSCC). *JCO*. 2019;37(suppl 15):6015-6015. doi:10.1200/JCO.2019.37.15_suppl.6015

50. Lee A, Duggan S, Deeks ED. Cemiplimab: a review in advanced cutaneous squamous cell carcinoma. *Drugs*. 2020;80(8):813-819. doi:10.1007/s40265-020-01302-2

51. Grob JJ, Gonzalez R, Basset-Seguin N, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase II trial (KEYNOTE-629). *J Clin Oncol*. 2020;38(25):2916-2925. doi:10.1200/JCO.19.03054

52. AHS, Cancer Control Alberta. UNresectable squamous cell carcinoma treated with avelumab and radical radiotherapy. a study to evaluate the efficacy and safety of the combined use of avelumab with radiation therapy for the treatment of unresectable cutaneous squamous cell carcinoma. *Clinicaltrials*. Published 2021. Accessed August 7, 2024. https://clinicaltrials.gov/study/NCT03737721