

Received: 2018.10.06
Accepted: 2019.01.03
Published: 2019.03.06

Uncommon Presentation of Metastatic Squamous Cell Carcinoma of the Skin and Treatment Challenges

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Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 80
Final Diagnosis: Metastatic squamous cell carcinoma of skin
Symptoms: Back pain • leg swelling • uti
Medication: —
Clinical Procedure: Immunotherapy
Specialty: Oncology





Objective: Unusual clinical course
Background: Squamous cell carcinoma is one of the most common keratinocytic skin cancers, the other being basal cell carcinoma. It is the second most common skin cancer after melanoma. Cutaneous squamous cell carcinoma is mostly a localized disease. The metastatic presentation is rare even in the presence of invasive disease. The metastatic potential depends on the presence of high-risk features at the time of diagnosis. Lung, liver, and bone are the frequent sites of metastasis. Local and locoregional disease undergoes excision with or without adjuvant radiation. However, we lack proper treatment paradigms for this metastatic disease.

Case Report: We are reporting a case of an elderly female with a history of high-risk localized cutaneous squamous cell carcinoma treated with complete local excision and radiation presenting 5 years later with extensive disease to the lung and liver, abdominal nodes, and spinal fracture. The patient was not a candidate for chemotherapy due to kidney failure. On the basis of ongoing separate trials on different immunotherapies, she was started on nivolumab.

Conclusions: Treating metastatic cutaneous squamous cell carcinoma is a challenge considering the absence of phase III trials due to the rarity of this disease. Historically, platinum with or without 5-FU (fluorouracil), bleomycin, doxorubicin, and retinoic acid were used with variable responses. Data on epidermal growth factor receptor (EGFR) inhibitors on EGFR expressing tumors are available. However, even with the most recent reports on immunotherapy in patients with high programmed death-1 expression or high mutation burden, it is difficult to achieve good response.

MeSH Keywords: Antigen, CD274 • Carcinoma, Squamous Cell • Fluorouracil • Immunotherapy • Programmed Cell Death 1 Ligand 2 Protein

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Background

Squamous cell carcinoma (SCC) is the second most common skin cancer [1]. There are an estimated 700 000 new cases diagnosed annually [2]. As these tumors are not included in national registries, actual data is not available. Most SCCs occur *de novo* or in the setting of precancerous lesion like actinic keratosis and Bowen's disease, which is associated with increased metastatic potential [3]. There is a 10% lifetime risk of incidence of SCC, which increases every year by a certain percent [4]. USPSTF (U.S. Preventive Services Task Force) has encouraged behavioral interventions to decrease exposure to sunlight and encourage skin self-examination to prevent the occurrences of malignancy in high-risk groups.

The most common carcinogen for skin cancer is sunlight. Genetic syndromes like albinism and xeroderma pigmentosum predispose to cutaneous SCC (cSCC) secondary to increased sensitivity to ultraviolet (UV) rays. It has been suggested that the p53 and RAS pathways play a pivotal role in malignant transformation [5]. It has been demonstrated that UV radiation is directly absorbed by DNA resulting in DNA damage causing both genetic and epigenetic changes in keratinocytes and dermal cells. UVB radiation from cumulative sun exposure induces mutations inactivating TP53 in almost 60% of cases. It is considered to be an early event as it is found in clusters of keratinocytes in sun exposed skin and actinic keratinocytes. UVA also has been shown to demonstrate increased incidence of cSCC with PUVA (psoralen and UVA light therapy) and tanning beds.

In recent years, understanding of the disease process has advanced to a more molecular level. RAS mutation is found in almost 3% to 30% of sporadic SCCs and 14% in patient treated with BRAF inhibitors [6]. Treatment-associated increased occurrence of cSCC was reported by Peng et al. in a melanoma patient undergoing treatment with BRAF inhibitors [7]. The reason for this event was reported to be due to paradoxical ERK activation or the hyper activation of ERK signaling by BRAF inhibitor in BRAF wild-type cells. It is thought that BRAF inhibitors contribute to the preexisting oncogenic process. These alterations allow keratinocytes to resist apoptosis. Furthermore, inactivation of another gene, CDK2A, is implicated in the malignant process. The mutation or hypermethylation of CDH2A was described in 35 primary and metastatic tumors [8].

The role of tumor micro environment was first mentioned in 1992 [9]. The perspective of the disease biology has been defined at the molecular level to identify a therapeutic target. The driver mutations are present in both malignant cells and sun-exposed keratinocytes. There is a new emphasis on alterations of dermal and stromal environment by the predisposing risk factors like UV rays [9]. Neoplastic cells expressing

proteinases, such as matrix metalloproteinases (MMP) and actinic keratosis, induce stromal fibroblasts and macrophages which contributes to the progression to invasive and metastatic disease. Collagen XV and XVIII is known to be involved in tumorigenesis and angiogenesis [10]. The varied expression of these collagens, type XV in tumor stroma and XVIII in tumor cells, are considered potential biomarkers in the disease. In addition, accumulation of inflammatory cells and increased expression of complement components and inhibitors by tumor cells (CFI complement factor I, CFH complement factor H, FHL-1 factor H-like protein 1) is reported to have some significance in pathogenesis of metastatic disease [11,12].

Siiskonen et al. described a Genome-wide Association Study (GWAS) of cSCCs among individuals of European ancestry that identified genetic *loci* associated with CSci risk [13]. The association of single nucleotide polymorphisms (SNP) of the class II human leukocyte antigen with tumor development was reported [14]. However, this data needs further validation.

Several cases have been reported showing the association with indoor tanning, scars [15], organ transplantation [16], chronic wounds (Marjolin ulcer), chronic draining fistula, chronic urinary irritation, and uterovesical stoma [17]. Other immunosuppressed state caused by chronic lymphocytic leukemia, lymphoma, or human immunodeficiency virus have been suggested to increase the prevalence of this disease.

Case Report

An 80 years old female with a medical history of hypertension and chronic kidney failure presented with left groin rash and swelling. Biopsies of the skin and lymph node were suggestive of poorly differentiated SCC with keratinization, positive for p40 and p63 (Figures 1, 2). One of the lymph nodes was positive for malignancy. Gynecological and gastroenterology evaluation was performed and anogenital origin of SCC was ruled out. The diagnosis of locally advanced cSCC was made. The patient underwent lymph node resection followed by adjuvant radiation.

Four years later, the patient presented to the Emergency Department with severe back pain and left leg swelling. Initial assessment showed hypercalcemia of 12.8, microcytic hypochromic anemia with (hemoglobin of 10.5 g/dL and MCV of 78.2 fL) and lytic lesions with compression fracture of T11. A left lower extremity duplex scan showed deep venous thrombosis. The patient was started on enoxaparin. Magnetic resonance imaging (MRI) of the thoracic/lumbar spine showed metastatic bony involvement at the area of T11, T12 with pathologic compression fracture of T11, and epidural extension of disease at both levels. Computed tomography (CT)

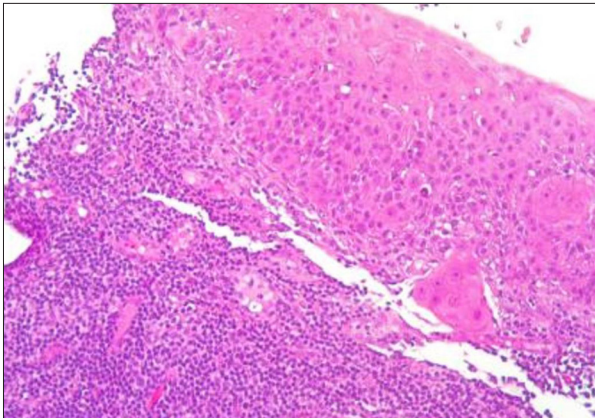


Figure 1. Lymph node under low power field.

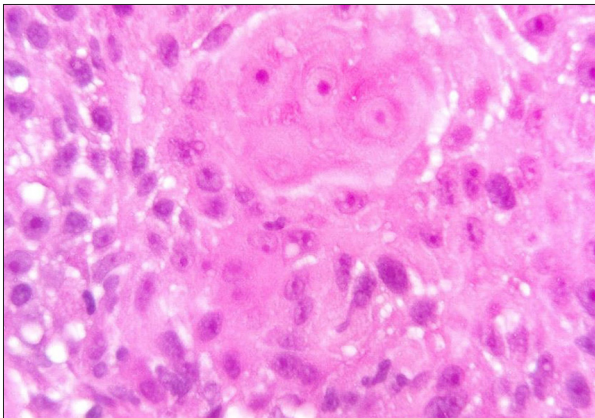


Figure 2. Lymph node under high power field.

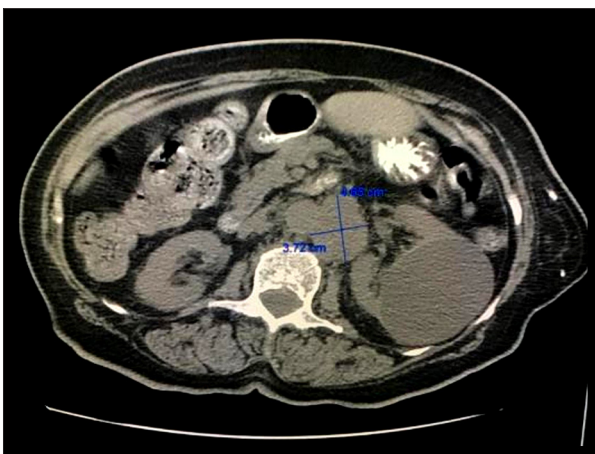


Figure 3. Computed tomography scan of the abdominal lymph node at time of metastatic disease.

scan of chest, abdomen, and pelvis without contrast showed extensive para aortic and pelvic lymphadenopathy (Figure 3) with lymph nodes measuring up to 3.6 cm in diameter and a pelvic mass (Figure 4). Multiple nodules, up to 7 mm in diameter, located throughout the lungs were compatible with metastatic disease.

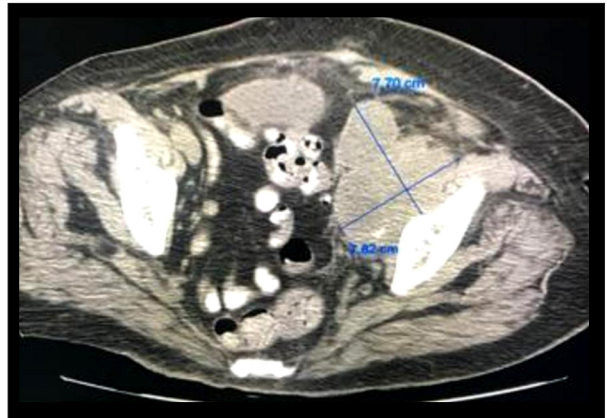


Figure 4. Computed tomography scan of left pelvic mass before treatment.

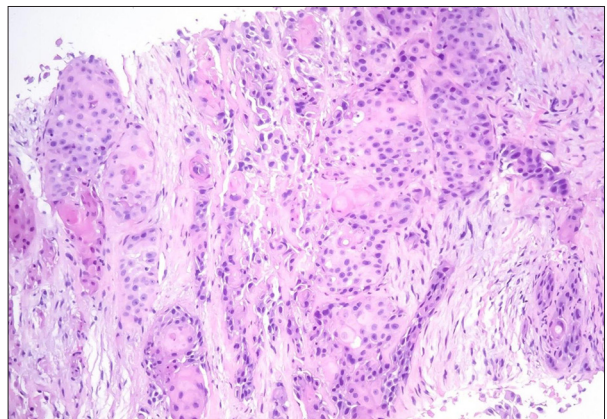


Figure 5. Biopsy of the supraclavicular node under low power field.

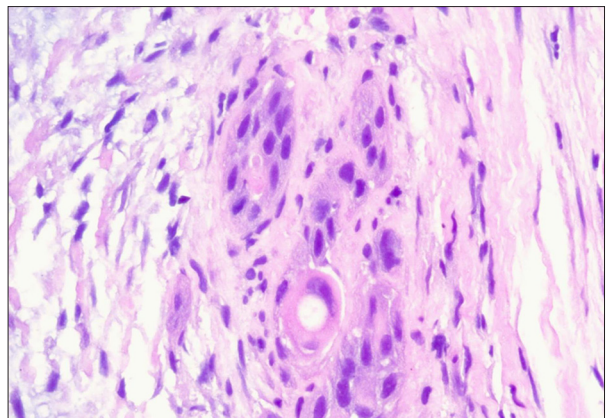


Figure 6. High power field of the supraclavicular lymph node showing keratinization.

Biopsy of left supraclavicular lymph node confirmed metastatic poorly differentiated SCC consistent with her previous biopsy from left groin (Figures 5, 6). The morphology and immunostaining were similar to the local SCC diagnosed 4 years earlier, i.e., positive for CK (cytokeratin) 903, p40 (Figure 7), and p63.

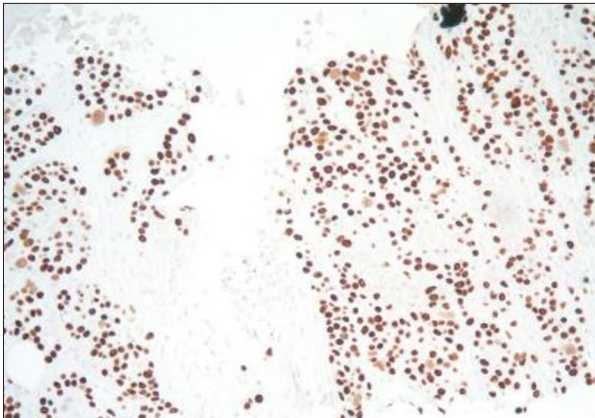


Figure 7. p40 positivity of the nodes.

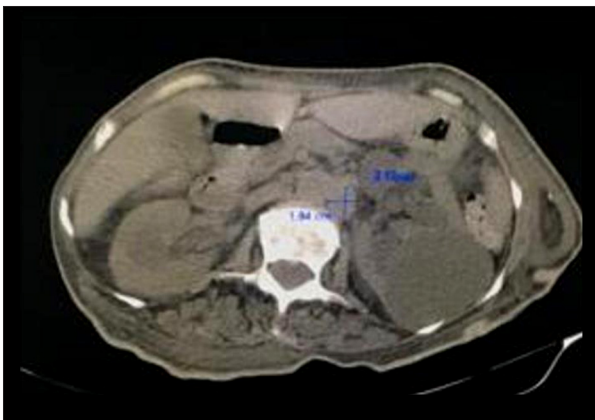


Figure 8. Computed tomography scan showing decrease in the size of the abdominal lymph node after 5 cycles of treatment.

The tissue was positive for programmed death ligand-1 (PD-L1) by 30% and negative for EGFR mutation.

She received palliative radiation to the thoracic spine for pain related to compression fracture. Due to her history of chronic renal failure and poor performance status (ECOG of 2) cisplatin was not an ideal choice.

Due to very limited options and extensive discussion with the patient and the family, she was started on nivolumab every 2 weeks. Clinically, the patient had very good response. The palpable lymph nodes resolved. After 5 cycles of treatment, CT scan abdomen showed decreased size of her abdominal lymph nodes (Figure 8) and prominent soft tissue extending along the left common iliac artery and into the left pelvis approximately 7.9×8.0×15.7 cm Hounsfield measurement of 10 consistent with cystic or necrotic areas (Figure 9).

Considering this as a good response, the patient continued with this treatment. However, the repeat scan after 9 cycles of treatment, showed an increase in the size of the pulmonary nodules.

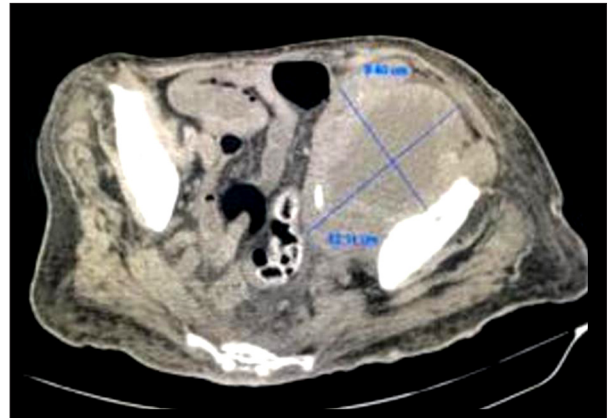


Figure 9. Computed tomography scan showing necrosis of the left pelvic mass.

The pelvic mass remained unchanged causing compression of her left pelvic veins and ureter, leading to repeated urinary tract infections and sepsis. A ureteral stent was placed with no symptomatic relief. After multiple admissions with sepsis, the patient deteriorated clinically and opted for hospice care.

Discussion

As mentioned earlier, squamous cell carcinoma (SCC) and basal cell carcinoma are collectively called non-melanoma skin cancer. SCC is more common than basal cell cancer with increasing incidence every year. Local cutaneous SCC (cSCC) has very good survival of >90% for 5-year survival. However, the survival in advanced disease decreases significantly.

In general, cSCC is staged earlier under the American Joint Commission on Cancer (AJCC) staging system-7 for cutaneous cell carcinoma and another cutaneous carcinoma [18] and as most cutaneous cell carcinomas occurred on the head and neck, the AJCC-8 guidelines cover carcinoma of head and neck, along with Merkel cell carcinoma and melanoma. Thus, the cSCCs, other than head and neck, do not have complete AJCC staging system available.

Metastatic potential was defined into 3 broad categories: clinical features, histology, and molecular biology. The combined high-risk features from these groups would identify patient with a risk of metastasis [19–21]. Clinical features are a subgrouped under predisposing genetic conditions like xeroderma pigmentosa, or premalignant conditions like Paget's disease, as well as immunosuppression, size of the lesion >2 cm with high increased risk of lymph node involvement; sites such as lip and ear with highest incidence and scalp and genital with medium risk. Histologic features include tumor thickness, degree of tumor differentiation, surgical margin, perineural invasion, and lymph vascular invasion with higher risk. Tumor thickness of

4 mm or less is considered a low-risk cSCC and a thickness of less than 2 mm is considered to have virtually no risk of distant disease. Histologic variants of cSCC with variable prognosis has been described, including keratoacanthoma (excellent prognosis), verrucous carcinoma, acantholytic adenoids, pseudovascular, adenosquamous and mucoepidermoid carcinoma, lymphoepithelioma-like, desmoplastic, spindle cell, invasive Bowen's disease, basaloid (aggressive), and warty carcinoma. Finally, molecular marker in cSCC are EGFR (epidermal growth factor receptor), p16, and CKS1B (cyclin dependent kinase regulatory subunit 1). EGFR expression is associated with more advanced disease and worse prognosis [22].

Even though the understanding of the disease pathophysiology has broadened, the treatment options for this metastatic disease remains limited [23–26]. The standard treatment for patient with localized disease is surgery or surgery followed by radiation and/or plastic reconstruction or Mohs' micrographic surgery or electrodesiccation or curettage. Non-surgical options include topical chemotherapy, topical immune response modifiers, radiotherapy, and systemic chemotherapy.

The advantage of adjuvant radiation after surgery has been widely debated in the past [27,28]. But multiple meta-analysis and retrospective studies has concluded high recurrence rate in the presence of positive lymph nodes, lymph vascular invasion, peri-neural involvement, positive surgical margin and poorly differentiated histology justifying role of adjuvant radiation. These studies demonstrated long-term survival including disease free survival, recurrence free survival and even overall survival.

The algorithm of treatment of metastatic disease does not exist [29]. Most of the literature are based on platinum-based therapy either alone or as in combination with 5-FU, bleomycin, Taxol, adriamycin, or vindesine [30,31]. A study that compared cisplatin and 5-FU versus surgery for local invasive cSCC concluded that cisplatin-based treatment was superior to surgery. Denic et al. in 1999 combined platinum compounds with bleomycin in patients with inoperable SCCs which improved tumor resectability [32]. Cartei et al. prospectively investigated the

efficacy of oral capecitabine in patients with SCC that had not been eradicated by surgery, radiotherapy, and topical 5-FU [33]. Capecitabine resulted in decreased the incidence of skin cancer in the patient with organ transplant [34].

The concurrent use of BRMs (biologics response modifiers) and chemotherapy was investigated in 2 phase II studies employing a combination of interferon alpha-2a and 13-cis-retinoid (13-cRA), with or without cisplatin resulting into some clinical activity in extensive locally advanced tumors [35,36].

Soon after the discovery of EGFR expression in these tumors, mostly in head and neck tumors, EGFR inhibitors constitute an important treatment option. Cetuximab is a chimeric human and murine anti-EGFR monoclonal antibody that has been studied in advanced SCC of the skin with and without radiation with variable results [37–39]. Other targeted therapy like erlotinib has been tried either as a single agent or with radiation [40,41]. Pan-HER inhibitor dacomitinib was investigated on locally advanced and metastatic cases with some durable response [42]. Some agents like herbacetin, a flavanol compound found in plants and wool hydrolysates, have been described with some benefits but are still at an investigational state [43].

The antitumor activity of checkpoint inhibitors in locally advanced and metastatic cSCC was established in phase I trial that was published in 2017 [44]. However, the clinical response in our patient was partial and short lived. In the current era of targeted therapy, biologics, and immunotherapy, treatment of metastatic SCC still remains a big challenge to the medical oncologist.

Conclusions

Metastatic cSCC is emerging as a not so uncommon disease with very poor prognosis. It is an extremely underestimated malignant entity with a lack of proper staging and standard treatment. Since we have a better understanding of the behavior of the disease, treatment options, including targetable agent, should be explored.

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