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Teaching Case

Neoadjuvant Cemiplimab Followed by Radiation for Locally Advanced, Unresectable Cutaneous Squamous Cell Carcinoma: A Case Report

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Introduction

Cutaneous squamous cell carcinoma (cSCC) is highly treatable with early detection and surgical resection.[1] However, locally advanced and metastatic disease have poor outcomes with surgery alone and require additional treatment. Historically, clinical trials in these disease states were not robust, consisting of case series, case reports, and small prospective trials. This led to a lack of general consensus regarding the use of adjuvant or neoadjuvant therapy.[2]

The high ultraviolet-related mutation burden of cSCC[3] may render it more susceptible to immunotherapy than other systemic therapy approaches. PD-1 inhibitors such as cemiplimab have emerged as a promising therapy.[4] Due to the results from the initial phase 1 and 2 studies, in which 61% of responses were durable at 6 months, cemiplimab was designated a breakthrough therapy.[5] A later phase 2 study by Gross et al showed that neoadjuvant cemiplimab before surgery led to a pathologic complete response in 51% of patients at the time of surgical removal.[6] Other case reports have discussed the neoadjuvant use of cemiplimab on cosmetically sensitive areas such as the lip,[7] or adjuvant use of cemiplimab after resection of a large, aggressive tumor on the scalp.[8] Although promising, there is little evidence to the efficacy of cemiplimab in multimodal treatment for patients who are not amenable to surgical resection.

Case Presentation

A 60-year-old uninsured woman with a pertinent medical history of chronic obstructive pulmonary disease, Hepatitis C, and tobacco abuse presented to the emergency department reporting pain and bleeding from a 12-cm fungating mass on the right forearm that had been growing for 3 years. In these 3 preceding years, she had treated the lesion at home with basic wound care and over the counter analgesics with up to 2000 mg ibuprofen every 6 hours. She also noted a 25-pound weight loss. She presented to the emergency department because of sensory changes and weakness in the right hand. Evaluation was then performed. See Fig. 1 for a clinical image of her right forearm lesion at presentation.

Skin biopsy revealed cSCC of the pseudoglandular variant. Computed tomography (CT) of the upper extremity showed a large, ulcerated arm mass with underlying muscle involvement, at least 12 cm in length encompassing 40% of the arm circumference. Magnetic resonance imaging (MRI) of the right upper extremity showed that the bulk of the mass was along the proximal forearm ulcerating through the subcutaneous fat and invading the brachioradialis muscle. There was no underlying bone involvement. See Fig. 2 for pretreatment MRI. CT of the

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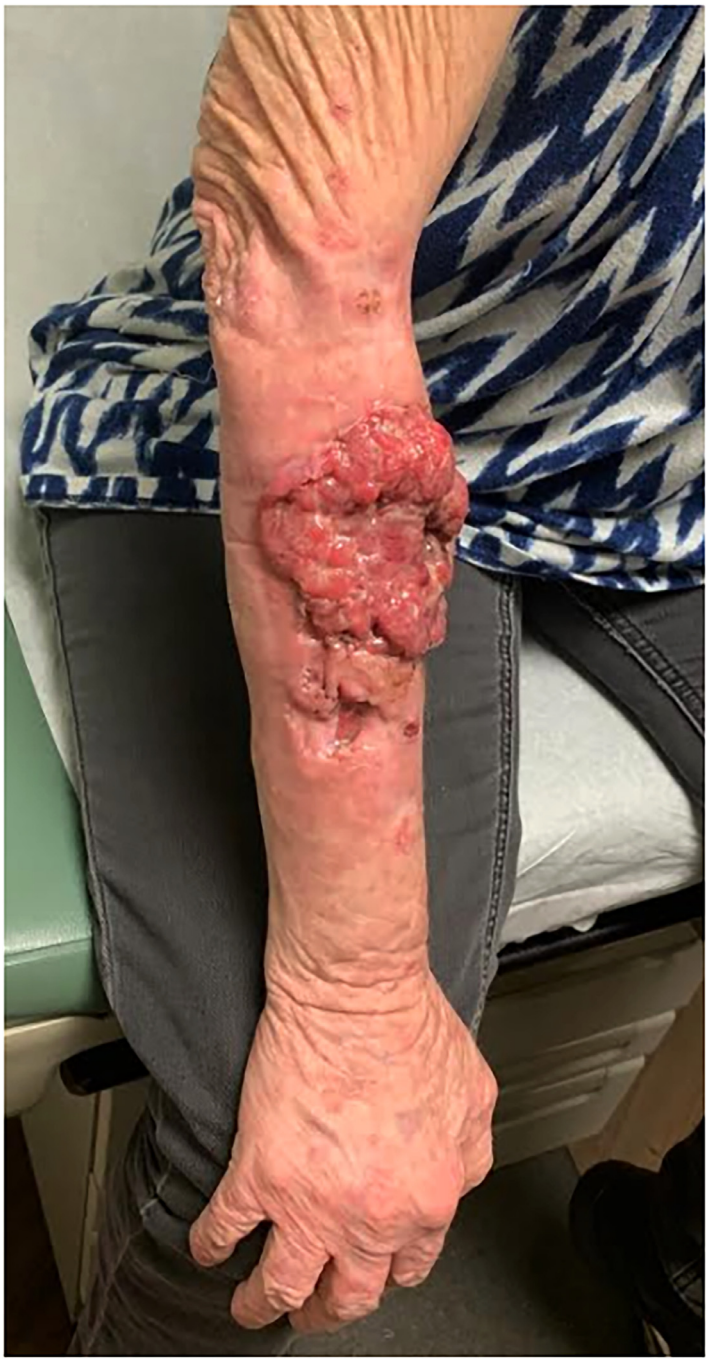

Figure 1 Pretreatment clinical image showing a fungating lesion on the right forearm with satellite nodules and ulcerations.

chest revealed a pneumonia versus small parapneumonic effusion of the right lung, and CT of the abdomen and pelvis revealed no acute abnormalities.

After a multidisciplinary discussion, upfront surgical resection was not pursued because the patient declined amputation. It was recommended she receive 4 cycles of neoadjuvant cemiplimab every 3 weeks followed by surgical resection and adjuvant radiation; however, the patient was noncompliant with appointments and interval restaging studies, and she received a total of 9 cycles of cemiplimab until all evaluations could be completed. Because of uncertain surgical margins and prior extent of disease, it was determined that she was not a good limb salvage surgical candidate due to expected morbidity, and

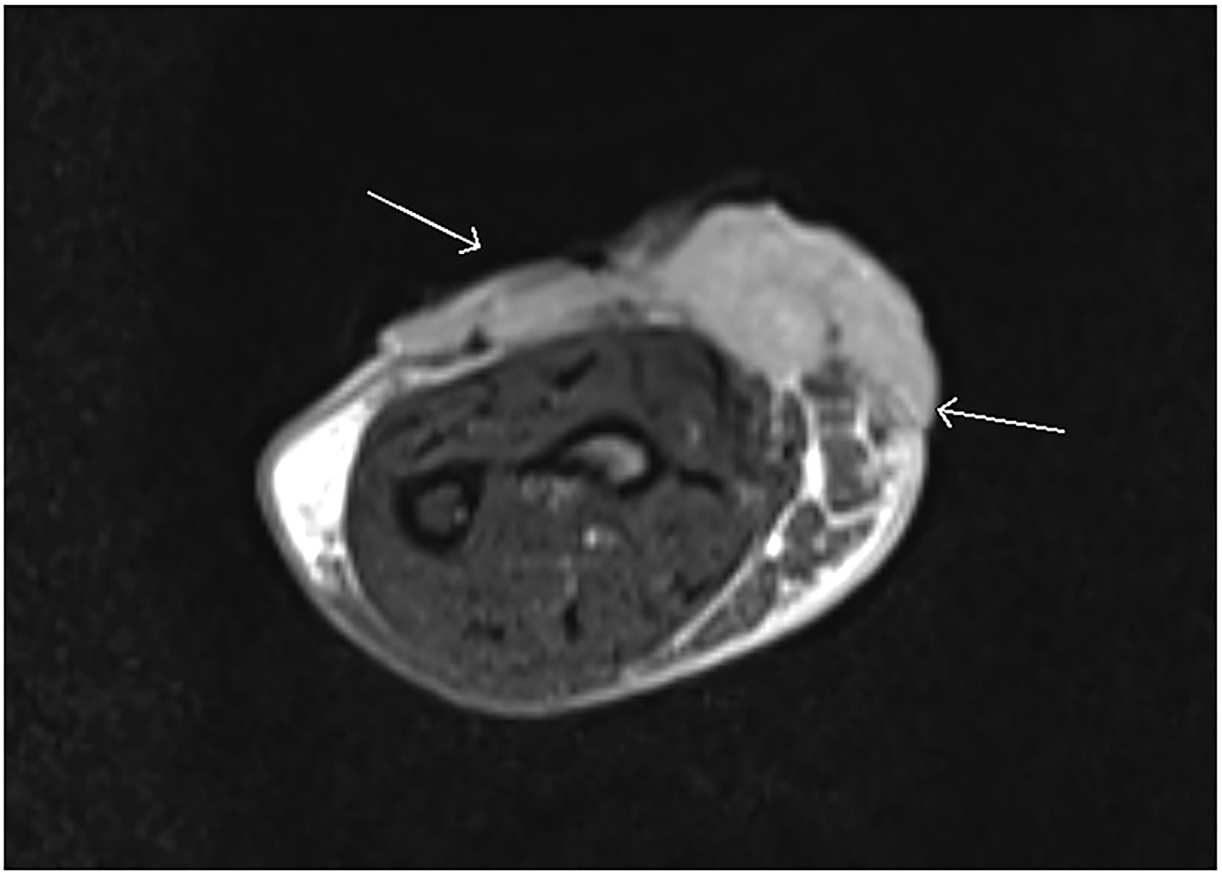

Figure 2 T2-weighted magnetic resonance imaging precemiplimab treatment axial slice showing ulceration through the subcutaneous fat and fascia with invasion into the brachioradialis muscle.

she instead underwent definitive radiation to a total dose of 60 Gy in 30 daily fractions.

CT simulation was completed in a prone position with right arm overhead using vaclok and custom thermoplastic mold for immobilization. Tumor bed and regions of initial involvement were treated with 60 Gy at 2 Gy per fraction. The plan was accomplished using 2 volumetric modulated arc therapy arcs with 6MV photons and daily 0.8 cm bolus conformal to the entire arm. Bone V40 was <60%. A 2 cm strip of skin was spared at least 20 Gy. There was some loss of planning target volume target coverage due to sparing bones and proximity to skin surface, although 95% of planning target volume was covered by 98.3% of prescribed dose. Daily cone beam CT was used to ensure accurate setup and reproducibility.

A partial clinical response was seen during the cemiplimab stage with radiographic resolution of muscular involvement. A complete clinical response was seen after completion of radiation therapy. The treatment course of cemiplimab was complicated by 2 hospitalizations due to bleeding, infection, hypokalemia, and iron deficiency anemia, which were medically managed. See Fig. 3 for post cemiplimab MRI and Fig. 4 for post cemiplimab clinical image.

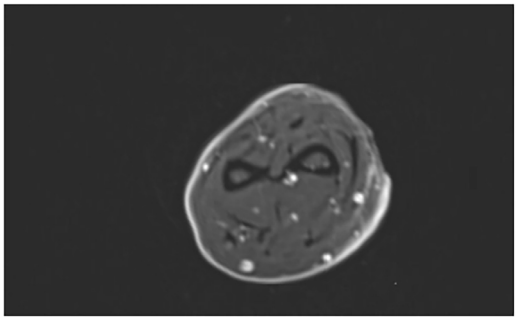

Figure 3 T2-weighted magnetic resonance imaging post cemiplimab treatment axial slice showing interval resolution of muscle involvement.

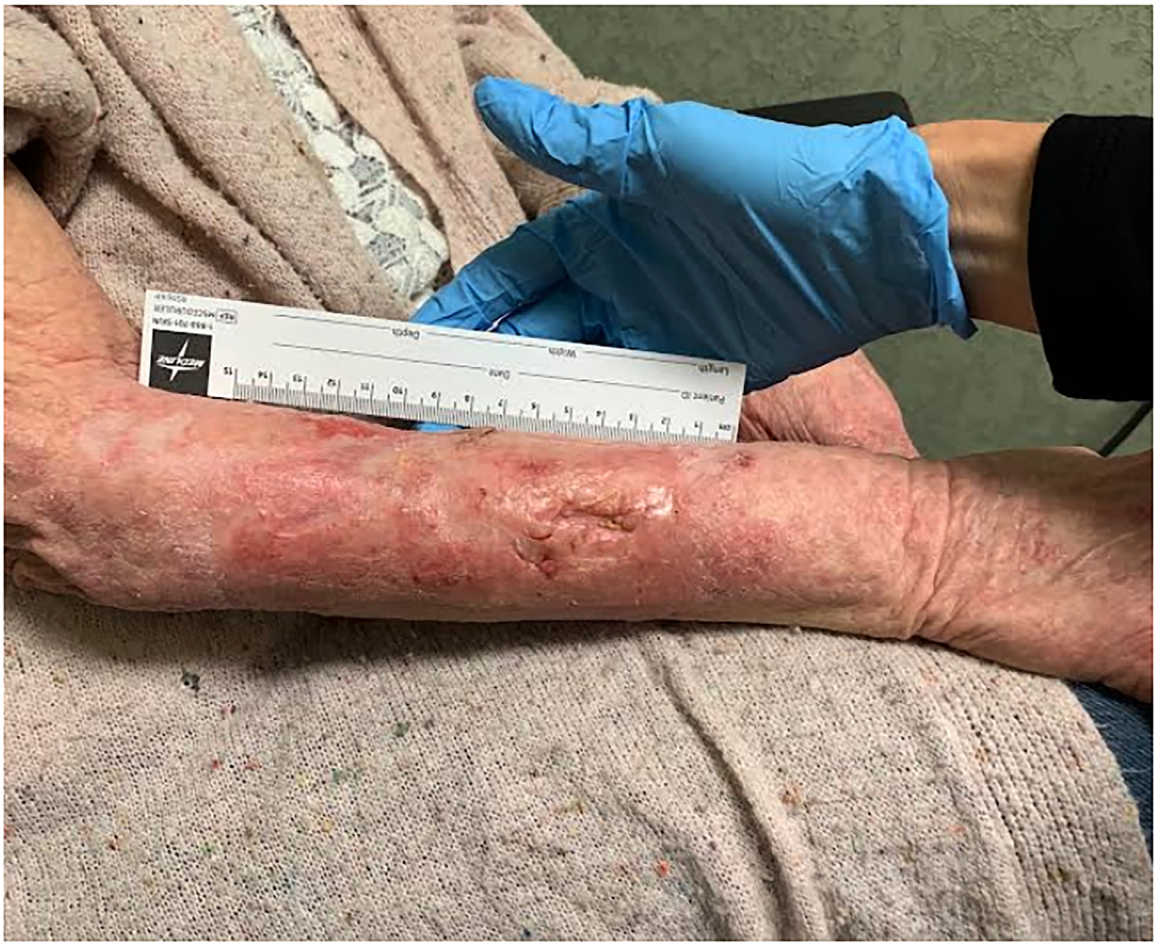

Figure 4 Post cemiplimab clinical image showing erythema and ulceration with resolution of fungating mass.

Throughout radiation therapy, the patient experienced grade 2 radiation dermatitis managed with assistance of a wound care clinic by applying sea salt strips over areas of desquamation as well as Plurogel, a surfactant-based topical gel, and Vaseline over the rest of the arm. The patient maintained her pretreatment Karnofsky performance status score of 80 and was able to continue working throughout the entire treatment course. Complete clinical response was maintained at 1.5-year follow-up with only mild sensory deficits over the original site of the tumor. See Fig. 5 for 1.5-year follow-up clinical image. See Fig. 6 for a detailed timeline of events from diagnosis to follow-up.

Discussion

There have been reports of concurrent cemiplimab plus radiation. Studies in 2020 showed that cemiplimab can be administered concurrently with radiation therapy without increasing adverse events and showed encouraging tumor response.[4] Furthermore, a study published in 2021 by Joseph et al described several patients who were started on cemiplimab with radiation therapy later added due to inadequate response. The study reports that the treatment was well tolerated with significant tumor response.[9]

These studies show that concurrent treatment could be a promising and viable therapeutic option; however, they differ slightly from the approach taken in this patient. In this case, we described a patient who received a full course of neoadjuvant cemiplimab before starting radiation therapy due to the patient's advanced presentation and socioeconomic limitations. Although not entirely unique, this case describes a previously undocumented treatment strategy that is important to consider as a viable option for future patients.

This case highlights the uncertain landscape of cSCC treatment and the complications that a patient's social history may present. Although surgical resection is the

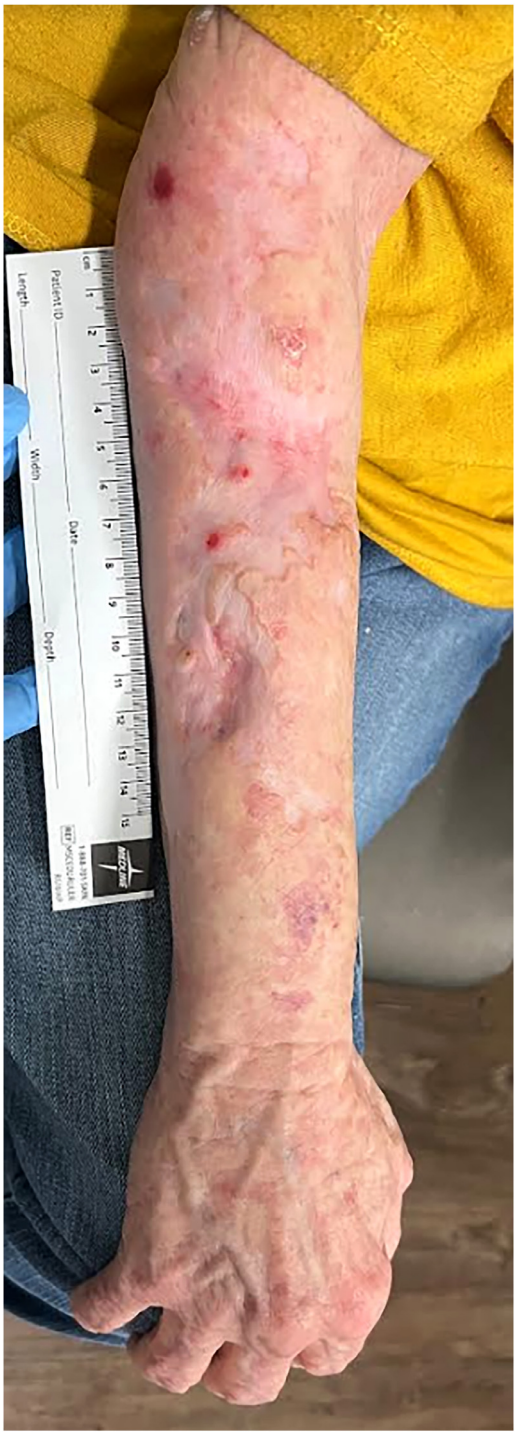

Figure 5 Follow-up clinical image at 1.5 years showing only tissue deficits.

mainstay for in situ or localized disease, treatment of locally advanced disease requires a multidisciplinary approach involving medical, surgical, and radiation oncology. In this case, surgical resection would have been far too radical because of the large and infiltrative lesion, and this novel approach was used. The durable complete response seen at 1.5 years after treatment is impressive and speaks to the potential that this treatment regimen may have in future patients. Additionally, the social issues that led to such an advanced presentation complicated the treatment course, contributing to the decision to use this novel regimen.

This case is a prime example of how a person's socioeconomic situation can have a massive effect on health care. With today's modern medicine, a cSCC should never progress to the extent seen in this patient. Perhaps the biggest contributor to this is getting patients into the office in the first place. A low health literacy and the lack of health insurance may have contributed to the advanced stage of the tumor at initial presentation. Unfortunately, uninsured patients who cannot afford proper medical care are often delayed in their presentation to a physician and ultimately require much more advanced treatments due to the bulk of their disease. Social issues were present and addressed throughout the patient's treatment. Health insurance was obtained during her treatment and a case worker was assigned at the conclusion of treatment, but the patient was still unable to afford follow-up imaging and was not able to attend any additional follow-up appointments.

Financial toxicity, the financial burden of cancer and its therapy,[10] was a major factor that influenced this patient's goals and plan of care. The patient needed to continue working throughout the treatment, and pain control and wound care management were emphasized. Absent workdays due to the symptom burden of cancer is part of the 2-hit model of financial toxicity, in addition to the outright expenses of treatment.[11] Additionally, this patient was uninsured through the first 4 cycles of cemiplimab, highlighting the importance of financial assistance programs to ensure prompt access to treatment. Still, even with financial assistance and access to social work, the costs associated with follow-up imaging and visits were too substantial.

Proposed solutions to financial toxicity include an automatic and universal referral system to a multidisciplinary team comprising social work, palliative care, and integrative medicine.[12] Theoretically, this would screen each patient for risks of financial toxicity and provide a concerted effort to address these and optimize the patient's care. However, the resources needed to universally refer to this supportive care team may not be available to all institutions. Finally, physicians should become comfortable having conversations with their patients in a nonjudgmental manner to normalize the topic.[13] The goal of these conversations is to prepare the patient and gauge

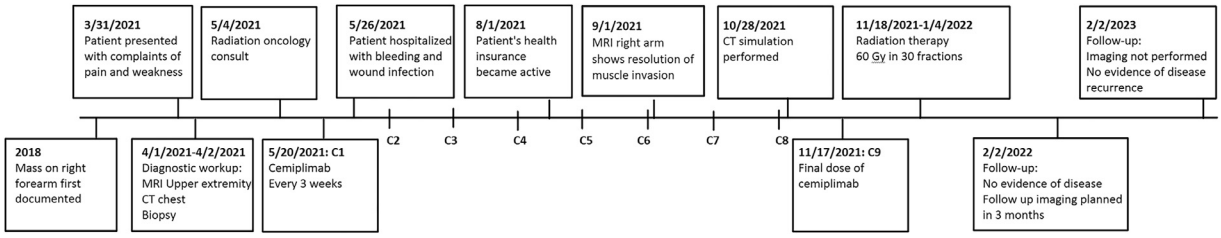

Figure 6 Timeline of patient presentation and treatment.

their understanding, not to deter from pursuing treatments because of cost.

Conclusion

This case describes a novel treatment approach for locally advanced cSCC, which has little consensus on standard therapies. Multidisciplinary planning and treatment, requiring medical, surgical, and radiation oncology was necessary. Neoadjuvant cemiplimab followed by radiation therapy was successful in treating a large fungating cSCC with infiltration into the muscle and created a durable clinical response at 1.5 years. The success of this case should be noted and further explored in future trials aimed at developing a standardized treatment approach. Additionally, social issues were prevalent and addressed to an extent throughout treatment, however these persisted and negatively affected the patient's follow-up.

Disclosures

The authors declare no potential conflicts of interest that would interfere with the interpretation and presentation of this research.

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