PROGRESSION OF IN SITU AND EARLY INVASIVE CUTANEOUS SQUAMOUS CELL CARCINOMAS WITH SUCCESSFUL TARGET TUMOR RESPONSE TO PD1 INHIBITOR THERAPY

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BACKGROUND

- The treatment of locally advanced and metastatic cutaneous squamous cell carcinomas (cSCC) is challenging. In many cases, the burden of disease is beyond what can be managed with surgery and radiation therapy.
- The medical management of unresectable tumors has historically defaulted to head and neck SCC protocols, resulting in unfavorable outcomes.
- In recent years, the anti-programmed cell death protein 1 (PD-1) antibodies, cemiplimab and pembrolizumab, received indications for advanced cutaneous squamous cell carcinoma by the Food and Drug Administration.
- PD-1 inhibitor therapy is quickly becoming the new gold-standard treatment for advanced cSCC through its ability to achieve more durable response rates as well as a more favorable side effect profile compared to chemotherapy and EGFR inhibitors.
- As the use of PD1 inhibitors for high-risk cSCC increases, an interesting phenomenon has been observed. Among responders, target tumors recede while superficial cSCCs remain unaffected and patients continue to develop new superficial and early invasive cSCCs on treatment.
- It appears that PD-1 checkpoint inhibition generates an adequate immune response in deep and/or metastatic cSCCs but permits the persistence and growth of new in situ and early invasive cSCCs.

OBJECTIVE

- To increase recognition of clinical outcomes associated with PD1 inhibitor therapy in order to enhance dermatologic evaluation and care for patients on immunotherapy for cSCC.

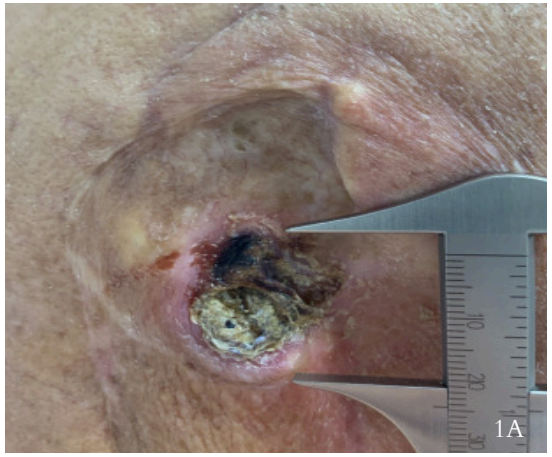
METHODS

- We observed a phenomenon related to PD1 inhibitor therapy in our case series of 4 patients (4 males; median age = 75.5 years [range 72-80]) with locally advanced or metastatic cSCC. Patients were followed in clinic every 3 weeks during cemiplimab (Patient 1-3) or pembrolizumab (Patient 4) infusions.

RESULTS

- All 4 patients experienced clinical improvement in their targeted locally advanced or metastatic cSCC tumors within one year of treatment.
- Three patients had complete clinical responses in their primary tumors within 1 year of PD1 inhibitor therapy and the remaining patient demonstrated significantly decreased enhancement in his target tumor on imaging.
- However, during or following PD1 inhibitor treatment, all 4 patients had new or persistent growth of squamous cell carcinoma in situ (SCCis) and early invasive cSCCs:
  - Patient 1 developed 2 new invasive cSCC lesions and had no response in pre-existing SCCis and actinic keratoses (AKs) of his head and neck.
  - Patient 2 developed 2 SCC-KA lesions and 3 cSCC lesions, 1 of which progressed from SCC-KA subtype to an early invasive cSCC.
  - Patient 3 developed 1 lesion of hypertrophic AK and 1 lesion of basal cell carcinoma (BCC) with partial squamous differentiation 3 months following completion of cemiplimab.
  - Patient 4 developed multiple hypertrophic AKs and a cutaneous horn while receiving pembrolizumab.

PATIENT 1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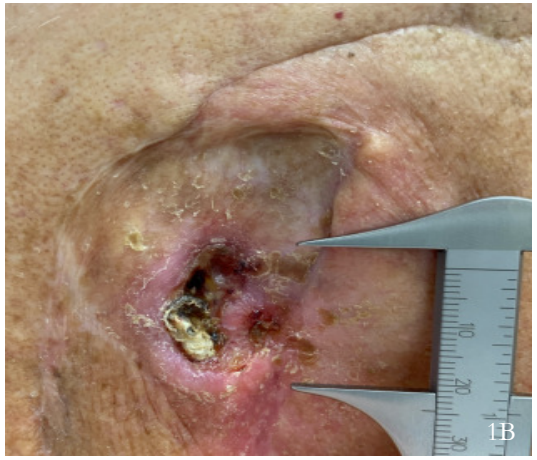
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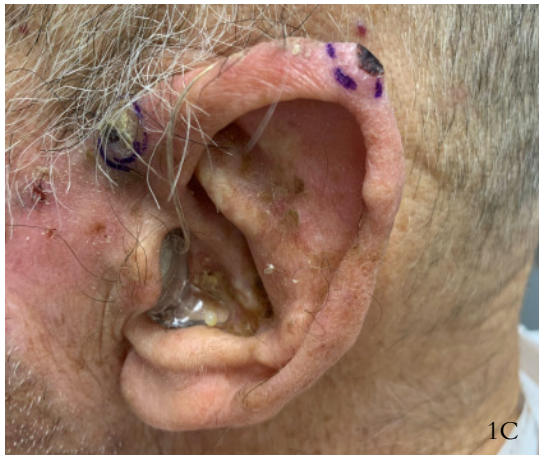
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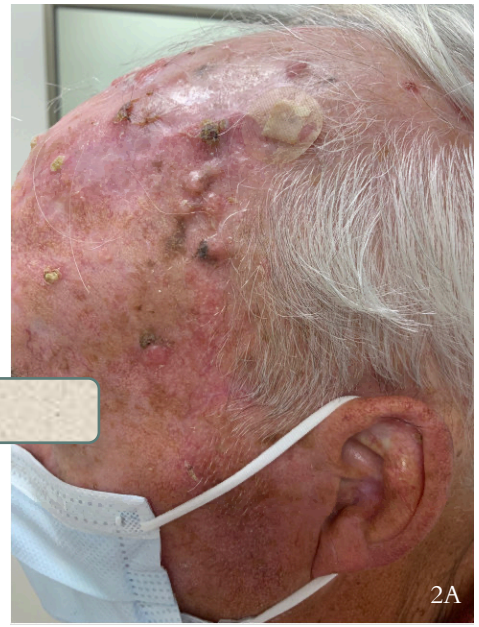
Patient 1: 72-Year-Old Male

- Figure 1A: Recurrent high-risk squamous cell carcinoma (SCC) (BWH stage T3) of the right ear before cemiplimab
- Figure 1B: Clinical improvement in high-risk SCC of the right ear during cemiplimab
- Figure 1C: Development of 2 new biopsy proven invasive SCCs of the left ear during cemiplimab

PATIENT 4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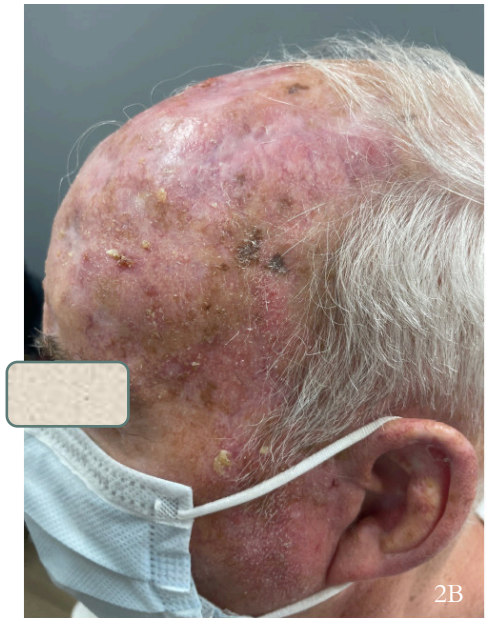
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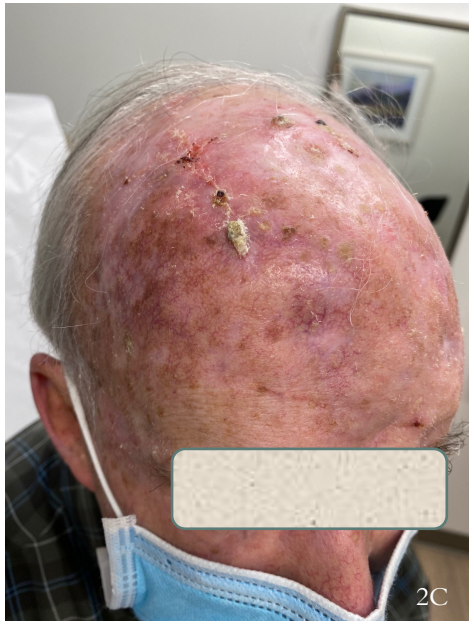
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Patient 4: 72-Year-Old Male

History of cutaneous squamous carcinomas of the right face for which he is s/p stereotactic body radiation therapy who presented with in-field recurrences.

- Figure 2A: Multiple subcentimeter cutaneous nodules (biopsy proven poorly differentiated SCCs) of the left parietal scalp without epidermal involvement prior to pembrolizumab. PET/CT reveals foci of FDG avid soft tissue uptake in left scalp c/w in-transit/satellite unresectable SCC metastases.
- Figure 2B: Clinical improvement in multiple left scalp SCC metastases during pembrolizumab therapy.
- Figure 2C: Development of 1 cm cutaneous horn (biopsy proven SCC in situ) on the right parietal scalp during pembrolizumab.

DISCUSSION

- Possible mechanisms for the variation in treatment responses include tumor biology and T cell recruitment factors.
- A high mutational burden from chronic UV damage makes cSCC very susceptible to immunotherapy with checkpoint inhibitors. Low rates of mutational burden found in early stage SCC may not be sufficient to generate an adequate T cell response.
- The persistence of in situ and locally advanced cancers could be due to a lack of immunogenic tumor antigens that are present in greater quantities in advanced SCCs.
- Early stage SCCs may not be sufficiently differentiated from their tissue of origin for sufficient T-cell recognition.
- T cell recruitment in the subcutaneous tissue is superior to that in the epidermis and upper to mid dermis. This effect could be attributed to local immunosuppressive factors in the more superficial compartments of the skin that are not present in subcutaneous tissue.

CONCLUSION

- The anti-programmed cell death protein 1 (PD-1) antibodies recently received indications for advanced cutaneous squamous cell carcinoma by the Food and Drug Administration:
  - Cemiplimab (2018)
  - Pembrolizumab (2020)
- We have observed that among responders to PD1 therapy for high-risk SCC, target tumors recede while superficial cSCCs remain unaffected and patients continue to develop new superficial and early invasive cSCCs on treatment.
- Our experiences suggest that PD-1 inhibitor therapy effectively targets deep dermal, perineural and subcutaneous cSCC tumors but fails to generate immune clearance of superficial cSCC.
- These observations raise questions about the immunogenicity of cSCC by stage, and the impact that PD-1 inhibition has on the superficial cutaneous microenvironment.

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