SKIN

BRIEF ARTICLE

Development of Multiple Facial Lipomas During Immunotherapy for Metastatic Squamous Cell Carcinoma

Kathryn Hall, PTA[1], Stephanie Han, MD[2], Adrian Guevara, MD[2]

[1] Burrell College of Osteopathic Medicine, Las Cruces, NM
[2] Epiphany Dermatology, Las Cruces, NM

ABSTRACT

An 85-year-old Caucasian male on immunotherapy for metastatic squamous cell carcinoma presented with enlarging lipomas in the area of his previous invasive squamous cell carcinoma of the lower lip and chin, status post resection, reconstruction and local radiation. The development of multiple lipomas during immunotherapy is a novel association which has yet to be reported in the literature. We discuss a putative mechanism of action of pembrolizumab-induced lipomas and describe the patient's clinical course.

INTRODUCTION

Immunotherapy, specifically PD-1 (programmed death receptor-1) inhibitors, has seen a massive rise in use since first entering the market in 2005. A more than 600% increase in clinical trials involving PD-1 and PD-L1 (programmed death ligand-1) inhibitors has been seen in recent years[1]. While selectively unlocking the power of the immune system has proven successful for many patients with otherwise intractable cancers, the secondary impacts of these drugs have yet to be fully elucidated. This case examines the possible role PD-1 inhibitor immunotherapy may play in the formation of lipomas in skin that has undergone surgery and radiation.

CASE REPORT

A 85-year-old Caucasian male with a past medical history significant for congestive heart failure, gastroesophageal reflux disease, arrhythmia with pacemaker placement, basal cell carcinoma of the lower lip during the 1970s and 1980s status post two wedge resections, presented in 2022 with a poorly differentiated invasive squamous cell carcinoma of the right lower lip. On further workup he was found to have had metastasis to three cervical lymph nodes in levels 1a, 1b and 2a for which the patient underwent surgical excision followed by 26 cycles of radiation therapy totaling 46Gy and treatment was discontinued due to severe mucositis and resultant inability to feed. Simultaneously he received 21 cycles of eight days of pembrolizumab immunotherapy. The patient elected to not continue with radiation therapy due to experienced side effects. The patient presented to the dermatology clinic three months after the lymph node dissection for a concern of two different masses growing along his left lower cutaneous lip **(Figure 1)** and a third in his right submandibular region **(Figure 2)**. Physical exam showed two firm,

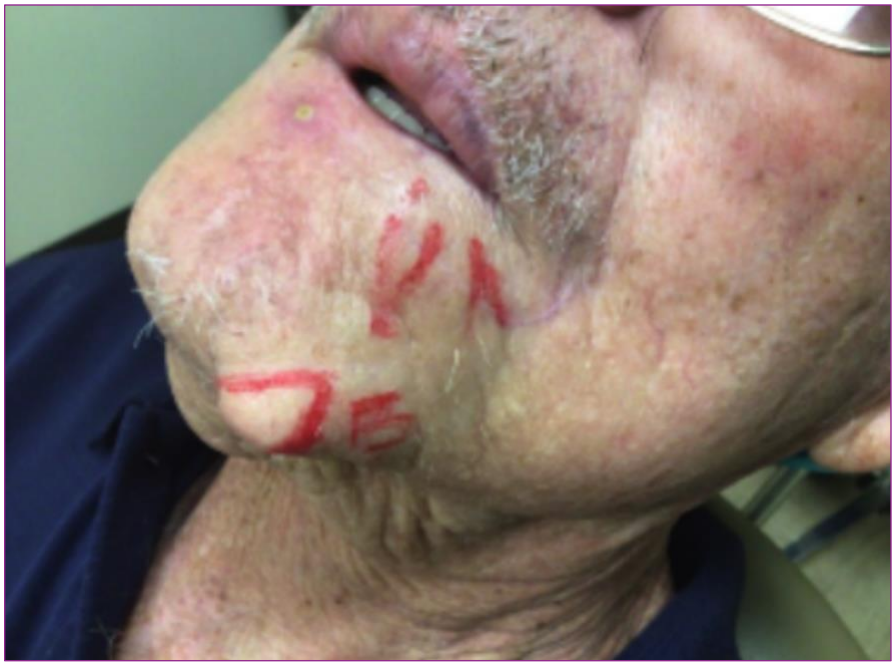

Figure 1. Image of patient's two lower lip and chin nodules (labeled A & B) prior to excision. Both were confirmed with pathology as lipomas.

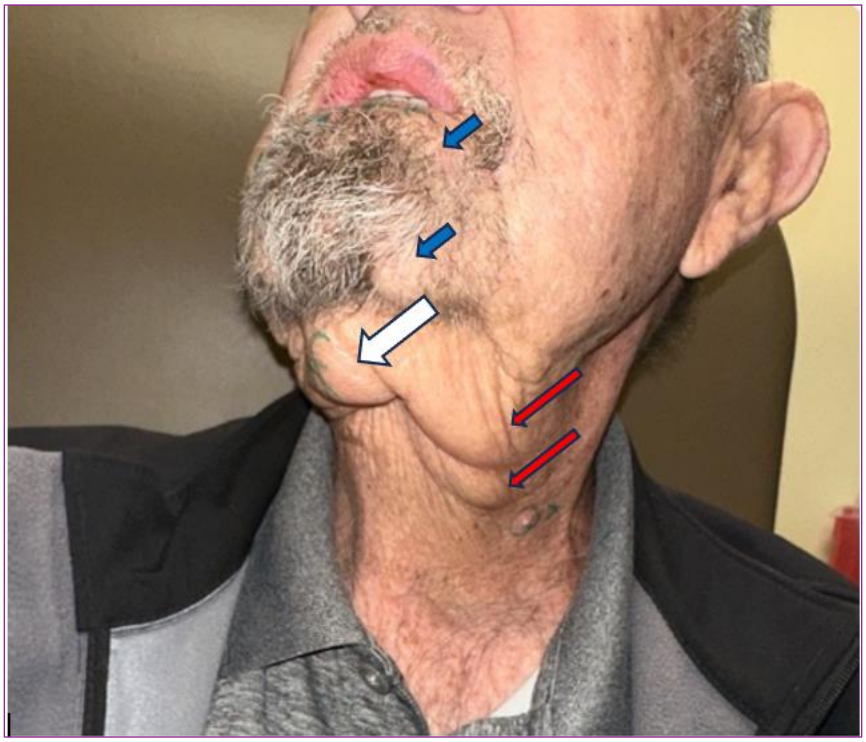

Figure 2. Punch biopsy confirmed the patient's submandibular mass (white arrow) was another lipoma. Short blue arrows designate the location of the patient's lower lip and chin lipomas as seen in Figure 1. Long thin red arrows identify lateral neck lipomas simultaneously present for which the patient deferred any management.

mobile and non-tender lower lip nodules measuring 1 cm in diameter each. The third mass in the right submandibular region was considerably larger but clinically similar to the other two. Lateral neck nodules were clinically identical to the other masses but the patient deferred addressing those nodules. The two lip lipomas were excised and confirmed with pathology. The third lipoma was confirmed with a punch biopsy, however its excision was deferred while other non-melanoma carcinomas, a melanoma in situ, and actinic keratoses were prioritized first.

DISCUSSION

With the rise in popularity of PD-1 inhibitor immunotherapy, the medical community is expected to see a rise in its unintended side effects. The side effect of multiple lipoma formation in our patient can most likely be attributed to the immunotherapy. This is because both the literature and common experience speak against surgery, radiation, or the combination of the two triggering lipomas. An extensive literature search found little to no evidence of lipoma formation triggered by surgery and/or radiation. We therefore investigated a possible mechanism of action by which a PD-1 inhibitor could trigger lipoma formation.

PD-1 is a cell surface receptor found on lymphocytes and plays a role in modulating the body's immune response. PD-1 inhibitors block the PD-1 receptor. Blocking this receptor on CD-8 T-cells disallows PD-L1 on tumor cells to connect to the receptor. Without that connection, the CD-8 T-cells recognize the tumor cell as foreign and target it for destruction[2].

The effects of PD-1 inhibitors extend beyond their eponymous receptor on CD-8 T-cells. Effective PD-1 blockade also promotes release of proinflammatory chemokines from a subset of helper T-cells, T follicular helper cells (TFH)[2], residing in both lymph nodes and tertiary lymph structures[3]. Tertiary lymph structures are ectopic lymph organs arising in non-lymphoid tissues secondary to chronic inflammation such as seen in malignancy[4]. The chemokine released by TFH[5] most salient to adipogenesis is chemokine ligand 13 (CXCL13)[6]. CXCL13 binds to a receptor CXCR5[7], on mature adipocytes to promote adipocyte differentiation[8]. Given that CXCL13 has been used as a marker of effectiveness in immunotherapy[9], it therefore follows that this chemokine in immunotherapy-responsive patients could trigger secondary lipoma formation.

The exact cause of typical lipoma formation to date remains unknown. Up to two-thirds are ascribed to genetic sources; the other third is attributed to trauma[10]. Post-traumatic lipomas may occur following a prolapse of local adipose tissue from blunt force or due to proliferation of adipocytes in the presence of chemokine release[11]. PD-1 inhibitor stimulated release of CXCL13 by TFH cells in the patient's labial tertiary lymph structures is posited to have contributed to his multiple lipoma development.

The surgery and radiation this patient received would have contributed to soft tissue inflammation, however neither intervention has proven to be a source of lipogenesis. Conversely, surgical removal is the definitive treatment for lipomas, and recurrence is rare with complete excision [10]. For atypical lipomas intractable to surgery, radiation has in fact been found to be an effective treatment[12]. As such, these authors would attribute this patient's sudden development of multiple lipomas to his immunotherapy course, not the surgery or radiation.

CONCLUSION

In this case report we present the first known description of secondary lipoma formation while on immunotherapy. While the connection between CXCL13 as a marker of immunotherapy response and as a potential stimulus for lipoma formation, further study is warranted to confirm this association.

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Corresponding Author:
Kathryn Hall
3866 Van Ess Ct,.Las Cruces, NM 88012
Email: Kathryn.hall@burrell.edu

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