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Neoadjuvant Immune Checkpoint Inhibition in Metastatic Conjunctival Melanoma

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Abstract

The development of immune checkpoint inhibitors (ICI) has transformed the treatment of advanced stage cutaneous melanoma; however, most trials did not include patients with conjunctival melanoma. Herein we describe a patient with recurrent conjunctival melanoma who developed locally advanced, BRAF-negative melanoma in her nasal cavity and extensive, metabolically active, bilateral lymphadenopathy in her thorax. Her nasal mass measured 4.3 × 1.7 cm and was determined to be unresectable. She was treated with four cycles of combination ipilimumab and nivolumab therapy followed by maintenance nivolumab. She experienced a dramatic treatment response with reduction in the size of her nasal mass to 3.0 × 1.1 cm and complete resolution of her adenopathy. She then underwent complete surgical resection of her residual mass (approximately 75% of her original tumor size) and remains melanoma-free at one year of follow-up. Given the underlying genetic similarities of conjunctival melanoma to cutaneous melanoma, providers should consider the use of neoadjuvant ICI for patients with locally advanced or limited metastatic disease.

Precis:

Here we describe a patient with metastatic conjunctival melanoma involving the nasal cavity and multiple lymph nodes who experienced a dramatic treatment response to immune checkpoint inhibitors, ultimately allowing complete surgical resection. She is now melanoma free one-year following her surgery.

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Introduction

Conjunctival melanoma is a rare but aggressive ocular malignancy with a reported incidence of 0.2–0.6 per million people. Originating from melanocytes in the conjunctival basal epithelium, conjunctival melanoma is a distinct entity from intraocular tumors such as uveal melanoma and is more closely related to cutaneous and mucosal melanoma[1]. The mainstay treatment for a localized conjunctival disease is surgical excision of the tumor followed by cryotherapy to the surrounding tissue. A no-touch technique is employed during excision of conjunctival melanoma such that direct manipulation of the tumor is avoided to prevent tumor cells from seeding into a new area[2]. Despite adequate treatment of the primary tumor, 60% of patients with conjunctival melanoma experience local recurrence[3]. Patients with conjunctival melanoma often develop dissemination of disease to the head and neck lymph nodes and other body sites with a reported 10-year overall metastasis rate of 19%[3]. To date, there is no standardized treatment algorithm for metastatic conjunctival melanoma[4].

Like cutaneous melanoma, conjunctival melanoma often harbors mutations in proto-oncogenes within the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling cascades. The most common driver mutations occur within the small GTPase, NRAS, and its downstream effector, BRAF, as well as within the tumor suppressor protein NF1[5]. These mutations independently result in constitutively active signaling leading to uncontrolled cell growth and are the focus in the development of targeted therapies[5,6]. One recent case-report showed successful neoadjuvant treatment with combined BRAF/MEK inhibition in a patient with BRAF/V600E mutated conjunctival melanoma[7]. However, BRAF mutations are only found in 35% of conjunctival melanoma[6,8,9]. Patients with unresectable or metastatic disease without BRAF mutations are typically treated with immune checkpoint inhibitors. Immune checkpoint inhibitors (ICIs) have revolutionized the prognosis of patients with metastatic cutaneous melanoma. These therapies work by blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and/or programmed death protein-1 (PD-1) thereby promoting tumor recognition[10,11]. The successful use of both single-agent and combination ICI has been demonstrated in the treatment of recurrent, locally-advanced, and metastatic CM[9,12–16].

ICIs have been shown to be successful in the management of unresectable locally advanced and metastatic conjunctival melanoma[9,12]. While these therapies have not yet been demonstrated in the neoadjuvant setting for conjunctival melanoma, they have be used for other tumor types, including cutaneous melanoma and non-small cell lung cancer (NSCLC)[17,18] to reduce disease burden and increase the likelihood of complete surgical resection. Here, we present our experience employing ICI in a patient with unresectable conjunctival melanoma involving the nasal cavity and lymph nodes which resulted in dramatic disease reduction and enabled tumor resection. All collection and evaluation of protected patient health information were HIPPA compliant. All research adhered to the tenets of the Declaration of Helsinki.

Case

A 60-year-old female with no past ocular history presented with a lesion on her left cornea and adjacent conjunctiva inferiorly and nasally. It measured 5.5 × 4.5 mm (Figure 1A–C). Excisional biopsy by a no touch technique followed by cryotherapy revealed AJCC stage IIA, superficially invasive melanoma. However, three years later she developed recurrent disease. She underwent re-excision at that time but unfortunately experienced multiple episodes of recurrence. Exenteration of the left eye was offered, but the patient refused. Additional treatments performed included re-excision, cryotherapy, and external beam radiotherapy. Ten years after her original diagnosis she began having multiple weekly nosebleeds. She presented for evaluation and was found to have a soft-tissue mass in her left nasal cavity measuring 4.3 × 1.7 cm (Figure 2A). Biopsy of the nasal cavity mass demonstrated BRAF-negative metastatic melanoma. PD1/PDL1 status was unfortunately not evaluated in this patient. PET scan at that time also showed extensive, metabolically active, mediastinal and bilateral hilar lymphadenopathy (AJCC TNM stage: T3dN1M1). While the lymphadenopathy was concerning for metastatic disease, given the distribution, granulomatous inflammation was also in the differential. Biopsy of these lymph nodes was not pursued as the nasal mass was felt to be unresectable and the only option for treatment of the nasal mass was systemic therapy. She was then started on first-line ipilimumab 1mg/kg and nivolumab 3mg/kg (dose as per Checkmate 511 due to concern for side effects with ipilimumab 3mg/kg)[19]. She did not experience any treatment-related adverse events and her epistaxis steadily improved. After completion of 4 cycles, she had approximately 25% reduction in the size of the nasal cavity mass to 3.0 × 1.1 cm (Figure 2B). She continued maintenance nivolumab. A PET scan 16 months into treatment showed near complete resolution of the mediastinal and hilar hypermetabolic lymphadenopathy, however the nasal mass persisted. She continued to have no evidence of disease outside the nasal cavity on scans for the next 8 months. Given the persistence of the nasal mass and lack of systemic disease, she underwent an endoscopic left medial maxillectomy. Pathology findings at that time were consistent with metastatic melanoma. Repeat CT scan after 7 months showed post-surgical changes without evidence of recurrence (Figure 2C). She passed away due to an unrelated cause but did not have any evidence of melanoma recurrence at one year follow-up.

Discussion

Multiple randomized controlled trials, including Checkmate-238, EORTC 1325, and IMMUNED, have evaluated the utility of ICIs in the adjuvant setting for cutaneous melanoma[20–22]. In these studies, recurrence-free survival ranged from 70–75% at one year and 63–70% at two years demonstrating that these agents can have lasting benefit[23]. Though the above trials did not include patients with conjunctival melanoma, the efficacy of ICIs in locally advanced and metastatic disease has been demonstrated in a handful of cases in the literature.

Two independent retrospective case series described the successful use of anti-PD1 therapy in the treatment of both locally advanced and metastatic conjunctival melanoma[10,12]. Of the five patients included in the series by Sagiv et. al, four patients had a complete response

and one patient had stable disease after 6 months of anti-PD1 therapy[9]. Similarly, two patients with metastatic conjunctival melanoma who were treated with either sequential or combination ICI had no evidence of disease two and three years after completion of therapy, respectively[12].

In another report, Chang et al. described a patient with orbitally invasive conjunctival melanoma and liver metastasis who had disease regression following combination ICI[16]. Combination ICI for 5 months in a different patient with locally advanced and metastatic conjunctival melanoma also showed dramatic reduction in tumor size and preservation of visual function[13]. While there are reports of ICI efficacy as an adjuvant or salvage therapy, to our knowledge there is only one report of its use in the neoadjuvant setting for conjunctival melanoma. In attempts to avoid orbital exenteration and disfigurement, Hong et. al, treated a patient with locally advanced conjunctival melanoma with 12 months of pembrolizumab. This patient experienced near total clinical resolution of their conjunctival melanoma with evidence of complete pathologic response, defined as the absence of residual viable malignant cells[13].

There are, however, studies that demonstrate efficacy of neoadjuvant ICI in advanced cutaneous melanoma[17]. For instance, an early study by Huang et. al, examined the usefulness of a single pre-operative dose of pembrolizumab in 27 patients with stage III and IV cutaneous melanoma. Major pathologic response was observed in 8/27 (29.6%) patients suggesting that even a short course of pre-operative ICI could provide clinical benefit[24]. These findings were further examined in randomized phase II study (SWOG 1801, NCT03698019)[25]. This trial demonstrated a significant improvement in event-free survival in patients with high-risk resectable melanoma who received neoadjuvant as opposed to adjuvant immunotherapy (HR: 0.59, 95% confidence interval (CI): 0.40–0.86)[25]. Other prospective studies examined the use of combination versus single-agent ICI in the neoadjuvant setting with high reported response rates for combination therapy (reported pathologic complete response (pCR), i.e. absence of residual viable malignant cells) ranging from 30–45%)[26,27]. The OpACIN trial (NCT02437279) also showed an increase in tumor infiltrating lymphocytes (TILs) following neoadjuvant treatment which is suggested to prolong relapse-free survival[27]. Unfortunately, TILs were not evaluated in the pathologic analysis of this patient's tumor before or after ICI. While no patients with conjunctival melanoma were included in these trials, the underlying genetic similarities and mutation profile between conjunctival melanoma and cutaneous melanoma suggest that patients with metastatic conjunctival melanoma may also benefit from neoadjuvant ICI therapy.

In the present case we describe one such patient that had a remarkable response to systemic immunotherapy. Her response converted her disease from unresectable to resectable and she underwent successful surgical resection. She remained melanoma-free at her 1-year post-operative follow-up.

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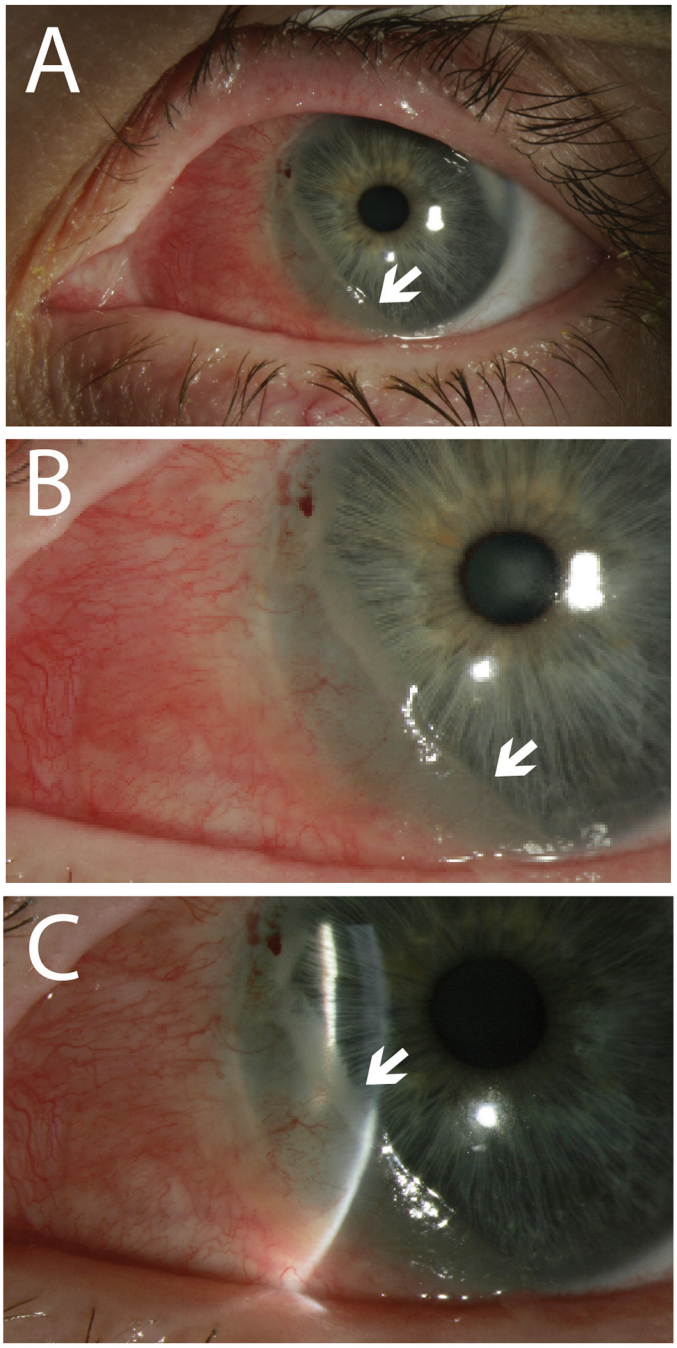

Figure 1.

Slit lamp photos of the left eye showing recurrent amelanotic conjunctival melanoma extending from the 6 o'clock meridians with intrinsic vascularity (white arrows) **(A, B)**. The conjunctival melanoma extends over the cornea nasally (white arrow) **(C).**

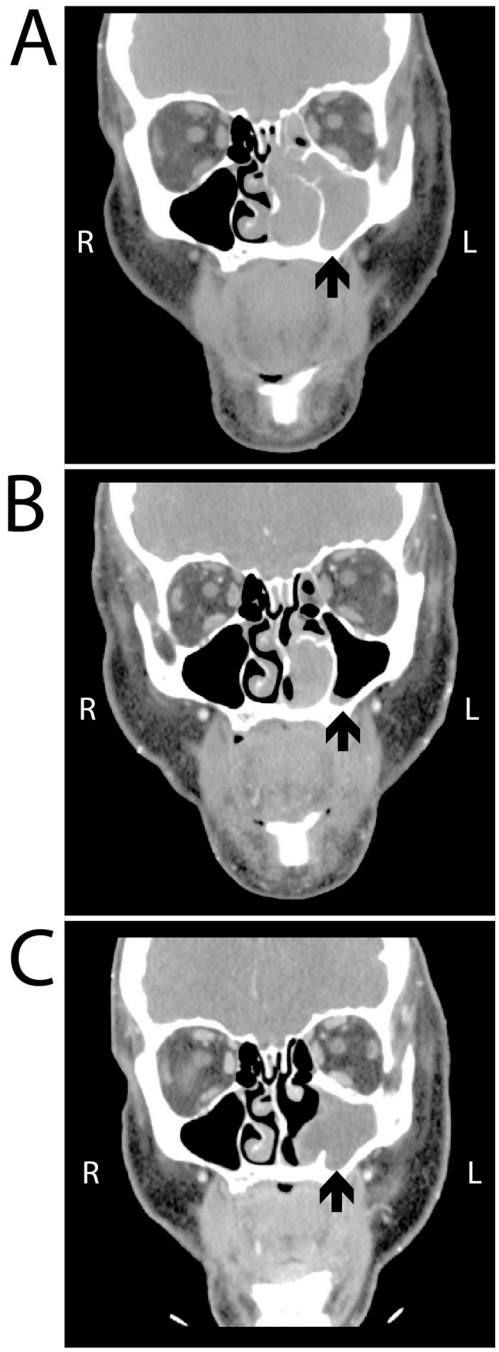

Figure 2.

CT images upon identification of a mass in the left nasal, ethmoid and maxillary sinuses **(A)**, after four cycles of combination ipilimumab/nivolumab, showing significant decrease in the size **(B)**, and at most recent follow-up imaging approximately 7 months post-op, demonstrating no recurrence but evidence of a polyp in the maxillary sinus **(C)**. Black arrows point out the mass in each image.