Acute Angle Closure Precipitated by Hemorrhage and Necrosis of a Large Uveal Melanoma in the Setting of Systemic Immunomodulatory Therapy

Chau M. Pham^a Krishna Kalyam^a Bradley T. Smith^b Justin Floyd^c
John B. Holds^d

^aDepartment of Ophthalmology and Visual Sciences, Washington University School of Medicine, and ^bThe Retina Institute, St. Louis, MO, ^cCancer Care Specialists of Illinois, Swansea, IL, and ^dOphthalmic Plastic and Cosmetic Surgery Inc., St. Louis, MO, USA

Established Facts

- The management of large uveal melanomas with documented metastatic disease upon presentation is not well delineated.

Novel Insights

- Hemorrhage and necrosis of large uveal melanomas, whether due to aggressive growth or as a response to systemic therapy, can cause significant morbidity.
- Primary enucleation of eyes containing large uveal melanomas with documented metastases at presentation may avoid potential morbidity related to hemorrhage and necrosis.

Keywords

Uveal melanoma · Acute angle closure · Tumor necrosis · Hemorrhage · Immunomodulatory therapy

Abstract

Management of nonmetastatic uveal melanoma has been well studied and a large body of work has been published by the Collaborative Ocular Melanoma Study (amongst many others). Management of uveal melanoma that is found to be metastatic upon initial diagnosis, however, is less well defined. We report an interesting case of acute angle closure caused by necrosis and hemorrhage into a large uveal melanoma occurring shortly after initiation of immunomodulatory therapy with ipilimumab and nivolumab for metastatic

disease. The use of these immunomodulatory agents in the setting of metastatic uveal melanoma is not well studied, and our case illustrates the importance of interdisciplinary communication in order to best decide the timing of surgical and systemic medical management to optimize outcomes and minimize morbidity.

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Introduction

Tumor necrosis and lysis can occur spontaneously when an aggressive tumor outgrows its blood supply but can also be precipitated by initiation of cytotoxic therapy for highly proliferative tumors with high disease burden

Fig. 1. a HE section. 40×. Extraocular extension of melanoma via the emissarial canal (arrow). **b** HE section. 40×. Extraocular extension of pigmented melanoma cells near an area of limbal perforation (limbal perforation not shown) (arrowhead).

such as acute lymphoblastic leukemia and Burkitt lymphoma [1]. Although systemic metabolic derangements caused by rapid cell death, known collectively as tumor lysis syndrome (TLS), can cause significant morbidity and mortality related to end organ dysfunction, local effects of tumor lysis and necrosis have the potential to cause significant morbidity as well. We report a case of secondary acute angle closure precipitated by tumor necrosis, inflammation, and edema closely following immunotherapy with ipilimumab and nivolumab for metastatic uveal melanoma. In this case, Tumor necrosis did not induce a metabolic derangement, but in the small and confined space of the eye resulted in a mechanically mediated acute angle closure and blind painful eye necessitating urgent enucleation.

Case Presentation

A 58-year-old Caucasian male with a medical history of hypertension and ocular history of left eye refractive amblyopia and choroidal nevus of the right eye was diagnosed with a large posterior uveal melanoma of the left eye. Exam on initial diagnosis was significant for count finger vision in the affected eye and a large pigmented choroidal lesion extending from 9:00 to 12:00 clockwise overhanging the macula, suspicious for uveal melanoma. B-scan showed a subretinal mass (20 × 20 × 14 mm) with low internal reflectivity and no extraocular extension. Systemic workup revealed hepatic metastases on PET/CT scan. Approximately 1 month after the diagnosis, the patient began systemic immunotherapy with nivolumab and ipilimumab followed by

enucleation after completion of the chemotherapeutic course. One week following the initial infusion with nivolumab and ipilimumab, the patient presented with acute ocular pain and worsening of vision to no light perception. He was found to have 360° angle closure with a flat anterior chamber and intraocular pressure of 40 mm Hg even after administration of 1,000 mg oral acetazolamide. B-scan showed a large mass occupying 75–80% of the globe and retinal detachment. He was admitted to the inpatient service for pain control and was subsequently referred for palliative enucleation of the blind painful eye. Intraoperatively, it was noted that there was hemorrhagic chemosis overlying an area of thinned and necrotic sclera with prolapse of pigmented material superiorly approximately 1–2 mm posterior to the limbus. Restaging MRI of the abdomen and CT chest obtained after the patient had completed 2 cycles of nivolumab and ipilimumab showed enlargement of the liver metastases and development of pulmonary metastases.

Histopathologic examination revealed a stage T4d melanoma [2] involving the choroid and ciliary body that measured approximately 23 mm in basal diameter and 14.5 mm in thickness. The tumor cells were mixed spindle and epithelioid cells with moderate amounts of mitotic figures, there was extraocular extension both via the emissarial canal and adjacent to an area of limbal perforation (Fig. 1a, b), and prelaminar optic nerve invasion. A focus of necrotic tumor abutted the lens/iris complex with associated apposition of the iris to the posterior cornea, consistent with the clinical history of angle closure (Fig. 2). There was hemorrhagic ischemia of the pars plicata adjacent to the tumor with prolapse of the iris and ciliary body into a limbal perforation correlating with the intraoperative observations. Examination of conjunctiva overlying and adjacent to this area found infiltration of necrotic tumor into the conjunctival stroma consistent with preoperative extraocular extension rather than protrusion due to mechanical manipulation at the time of surgery (Fig. 3).

Fig. 2. HE section. 20 $\times$. A large tumor with necrosis and hemorrhage abuts an artifactually absent lens, causing anterior displacement of the lens-iris complex, apposition of the iris to the posterior cornea, and mechanical angle closure (the lens was expelled during processing). Areas of hemorrhage and necrosis within the tumor body (arrows). Apposition of the iris to the posterior cornea (arrowheads).

Fig. 3. HE section. 40 $\times$. Conjunctiva submitted as a separate specimen. This conjunctiva was taken from an area overlying and adjacent to the area of limbal perforation and shows infiltration of pigmented melanoma cells into the conjunctival stroma (arrows).

Discussion

Uveal melanoma is rare, but is the most common adult primary intraocular malignancy with a 10-year cumulative rate of metastases in up to 38% for patients with large tumors [3]. Prognosis with metastatic disease is poor with a death rate of 80% at 1 year and 92% at 2 years, and a median survival of 12 months [3, 4]. Systemic therapy with chemotherapeutic agents commonly used in the treatment of metastatic cutaneous melanoma has not been shown to be particularly effective at improving overall survival for metastatic uveal melanoma [5, 6]. Currently, the most common treatment for uveal melanoma without evidence of metastases is local treatment with iodine-125 plaque brachytherapy for medium sized tumors and enucleation for large sized tumors [7]. Treatment of tumors with evidence of metastatic disease at initial diagnosis is less clear-cut, however, and the optimal timing of enucleation in relation to any systemic chemotherapeutic or immunomodulatory therapies is not known. In the present case, metastatic disease (isolated to the liver) was present at the time of diagnosis, and ocular disease was overall stable. In this case, immunomodulatory therapy was started as soon as possible in order to optimize any therapeutic effect, prevent further metastatic spread, and optimize survival benefit.

The use of immunomodulators has recently seen success in the clinical management of metastatic cutaneous melanoma. Ipilimumab is a monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 which enhances anti-tumor immunity and has been found to improve overall survival in unresectable metastatic cutaneous melanoma [8]. Nivolumab is a newer immunomodulator that targets an immune checkpoint molecule, anti-programmed death-1, that has been approved for use in combination with ipilimumab [9]. Clinical trials for these 2 agents originally excluded patients with metastatic uveal melanoma and their efficacy in this context is currently under study. Some studies have found that ipilimumab produced durable responses in patients with pretreated or treatment-naïve metastatic uveal melanoma with 1 study finding 31% survival at 1 year [10, 11], while other studies have found limited clinical activity or no objective responses [12, 13]. Clinical trials with nivolumab for metastatic uveal melanoma are currently recruiting participants [14]. Adverse effects of these 2 drugs are most commonly immune-related reactions in the gastrointestinal, hepatic, integumentary, or neurologic systems [15, 16]. According to the prescribing information, TLS is reported to be an uncommon adverse event ($\geq 1/1,000$ to $< 1/100$) with the use of ipilimumab at the

standard recommended dosing with only a handful of instances reported, while it has not been reported with the use of nivolumab [15–19]. Presumed TLS was documented in only 1 of 643 patients in a study of immune-related adverse events related to ipilimumab, while another study of 752 patients identified focal necrosis of an iliac lymph node metastases in 1 patient after salvage therapy with ipilimumab [18, 19]. It is too early to tell what other adverse events may be caused by the novel application of these therapies and further study is necessary and ongoing.

In our patient, histopathologic analysis of the enucleated globe is consistent with acute angle closure precipitated by the local mechanical effects of tumor necrosis. Temporal proximity within 1 week of initiation of immunomodulatory therapy is suspicious for tumor necrosis, subsequent angle closure, pain, and palliative enucleation, all precipitated by the systemic treatment. However, the enlargement of liver metastases and new pulmonary metastases after completion of 2 cycles of immunomodulatory therapy indicates that in this case, tumor

necrosis was more likely to be due to an aggressive tumor rather than the effects of systemic therapy. No matter the inciting event, this case demonstrates that tumor necrosis can precipitate events leading to significant morbidity. Timing of enucleation (if it is to be performed at all) in relation to initiation of any systemic therapeutics remains a management dilemma and illustrates that close communication between ophthalmic plastic specialist, retina specialist, and oncologist is imperative in the management of these patients.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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