CASE REPORT

Pembrolizumab dramatically resolves choroidal metastasis from esophageal adenocarcinoma and restores vision: a case report

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Abstract
Esophageal adenocarcinoma historically is an aggressive cancer with poor long-term survival. Ocular metastasis secondary to gastrointestinal malignancy is rare. In managing patients with ocular metastasis, quality of life (specifically vision preservation) is one of the most important factors patients and providers consider when deciding on a treatment regimen. Anti-programmed cell death-1 (PD-1) and PD-1 ligand (PD-L1) inhibitors such as pembrolizumab have shown promising results as second-line therapy for patient with metastatic malignancy. We describe a novel case of a functionally monocular patient with known metastatic esophageal adenocarcinoma who developed poor vision and a large choroidal lesion in his better seeing eye. The lesion regressed and vision restored to 20/20 after treatments with pembrolizumab in this case report.

INTRODUCTION

Ocular metastasis from systemic malignancy is the most common type of ocular tumor and noted in 12.6% of cancer patients on post-mortem examination [1]. Choroidal metastasis may be a presenting sign of primary or recurrent malignancy, portends very poor survival rates, and is frequently associated with significant visual impairment [2]. Ocular metastases are present in up to 4% of patients with primary gastrointestinal malignancies [3], most commonly arising from the lower GI tract and rarely from the esophagus [4-6]. Esophageal adenocarcinoma has a particularly poor prognosis with an approximate 5-year survival rate of 22% [7], despite treatments including surgical resection, radiation therapy and cytotoxic chemotherapy [2, 8]. Quality of life in these patients is severely compromised during aggressive therapy. Vision preservation is frequently reported as one of the most important quality of life indicators [9, 10].

The introduction of programmed cell death-1 (PD-1) and PD-1 ligand (PD-L1) inhibitors (such as pembrolizumab) in recent years have shown promising data in the treatment of esophageal cancer [9]. We present a novel case of a patient with known esophageal adenocarcinoma who was found to have a new onset choroidal metastasis. The patient was treated with pembrolizumab with rapid visual improvement to 20/20 and complete resolution of the uveal mass.

CASE REPORT
An 83-year-old Caucasian man with a history of a branch retinal vein occlusion (BRVO) with macular edema (receiving as-needed intravitreal bevacizumab injections in the right eye and advanced open-angle glaucoma with poor vision in the left eye) presented with new vision complaints. Six months earlier at
his previous visit, his visual acuity was 20/20 with resolved branch vein occlusion. He described gradual painless loss of a half-moon of central vision in the right eye over a three-month period. Past medical history was pertinent for known recurrent HER2 receptor positive esophageal adenocarcinoma with metastases to the liver and right pleural base as well as poor cardiac and functional status of 24-month duration. He was previously treated with carboplatin and paclitaxel infusions 11 months earlier and completed local radiation to the primary esophageal mass 13 months earlier.

Best-corrected visual acuity (BCVA) was 20/150 in the right eye and 20/400 in the left eye. Intraocular pressure was 10 mmHg in the right eye and 12 mmHg in the left eye (normal range 10–25 mm Hg). Anterior segment slit lamp examination was unremarkable in both eyes. Posterior segment examination of the right eye was notable for a 10.5-sq-mm choroidal lesion centered along the inferior temporal arcade extending into the inferior macula with serous retinal detachment of the macula (Figs 1A, 2A and 3A) with no additional lesions noted in either eye. In view of patient’s medical history, the mass was presumed to be choroidal metastasis secondary to esophageal adenocarcinoma. Local and systemic treatment options including proton beam irradiation and immunotherapy were discussed with the assistance of the oncology team. Ultimately, immunotherapy with pembrolizumab was selected to treat the lesion to preserve vision and maintain superior quality of life.

The patient was initiated on 200-mg intravenous pembrolizumab therapy every 21 days with the first dose administered three weeks after initial ophthalmologic evaluation. The patient was seen for ophthalmology follow-up one day after the second infusion. BCVA had improved to 20/40–1 in the right eye with marked decrease in size of the choroidal lesion and serous retinal detachment (Figs 1C, 2B and 3B). At 15 weeks following initiation of pembrolizumab infusions the patient’s visual acuity improved to 20/20 (Figure 3B). The lesion height regressed completely (4.4–0.7 mm) and became hypopigmented (Figs 1D and 2C).

**DISCUSSION**

Ocular metastases are present in up to 4% of patients with primary gastrointestinal malignancies [3], most commonly arising from the lower GI tract and rarely from the esophagus [4–6]. Metastases from lung and breast cancer are the most common, present in up to 26 and 37% of patients with primary lung and breast cancer, respectively [3].

Esophageal adenocarcinoma has a particularly poor prognosis with an approximate 5-year survival rate of 22% [7], even with treatments including surgical resection, radiation therapy and cytotoxic chemotherapy [2, 8]. Esophageal adenocarcinoma metastasis represents less than 1% of all choroidal metastatic lesions. Choroidal metastasis can present as a challenging treatment dilemma depending on characteristics of the mass, extent of systemic disease, treatment goals of the patient and availability of treatment modalities [2]. Date et al. reported an excellent outcome in a patient with recurrent metastatic esophageal adenocarcinoma treated with intensity-modulated radiation therapy in conjunction with 5-fluorouracil and trastuzumab [6]. Other reports of choroidal metastasis of esophageal adenocarcinoma have been treated with external beam irradiation, cytotoxic chemotherapy and enucleation with variable improvement of visual symptoms but inevitable death from the systemic complications of the primary malignancy [2, 3, 6]. Quality of life is often compromised from these aggressive therapies. Reports of the use of pembrolizumab in patients with secondary choroidal metastasis have been described only in cases with primary cutaneous melanomas [7], with no reports of its use in the setting of choroidal metastases associated with esophageal adenocarcinoma.

PD1 expression and ligation to PD1 in neoplastic cells results in a transduction of signals that allows for evasion of neoplastic cells from T-cell mediated immune response. By blocking this interaction, PD1 inhibitor immunotherapy such as pembrolizumab has become integral in the approach to treating cancers [9]. The safety profile of PD-1 inhibitors continues to be under investigation, though it has been shown to have less adverse events than traditional cytotoxic chemotherapy for advanced esophageal carcinoma [6]. Adverse events from anti-PD-1 therapy are thought to occur via excessive activation of CD4 and CD8 T cells, which result in excessive inflammation in normal tissues. In a large meta-analysis of patients treated with anti-PD-1 therapy for advanced gastro-esophageal cancer, no major ocular-specific complaints were noted [8]. However, cases have described inflammatory ocular sequelae of pembrolizumab including serous retinal detachment, choroidal effusion and detachment, and posterior uveitis, including birdshot-like choroidopathy and retinal vasculitis [10]. In one particular case of metastatic cutaneous melanoma without ocular metastasis, after three months of pembrolizumab infusions the patient developed isolated biopsy-confirmed vitreous metastasis that was thought to be caused by pembrolizumab-mediated retinal vascular leakage.

In conclusion, pembrolizumab successfully and rapidly decreased the size of choroidal metastasis, restored vision without any adverse events and improved quality of life. PD-1 and PD-L1 inhibitors offer promising treatment outcomes with improved side effect profile compared to traditional cytotoxic chemotherapy. Our patient demonstrated rapid improvement of lesion size and visual acuity without any adverse events observed at six months of follow-up.
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Figure 2: (A) B-scan ultrasound of the right eye demonstrating 4.39 mm height by 10.95 mm base choroidal lesion. (B) B-scan ultrasound of the right eye seven weeks after initiation of pembrolizumab demonstrating decreased lesion size 2.43 mm height by 10.05 mm base. (C) B-scan ultrasound of the right eye four months after initiation of pembrolizumab demonstrating further reduction in lesion size 0.74 mm height by 2.15 mm base.

Figure 3: (A) OCT of the right macula on initial presentation illustrating large intraretinal and subretinal fluid. (B) OCT of the right macula seven weeks after initiation of pembrolizumab demonstrating resolved macular edema and subretinal fluid.

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