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Intratumoral bacteria in uveal melanoma: A case report

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ABSTRACT

Purpose: Intratumoral bacteria and their potential application to cancer immunotherapy have been a topic of interest in recent studies. To our knowledge, bacteria in uveal melanoma have not been previously reported.
Observations: We describe a patient with a large choroidal melanoma, measuring 18 × 16 mm in basal dimension and 15 mm in ultrasonographic thickness, managed by plaque brachytherapy. At the time of plaque removal, a prophylactic scleral patch graft was placed to protect from anticipated scleral necrosis. Progressive ocular ischemia led to a blind and painful eye. The enucleated eye demonstrated an extensively necrotic and heavily pigmented mushroom-shaped regressed cilichoroidal mass deep to the scleral patch graft. Numerous Gram-positive cocci were noted within the regressed uveal melanoma and the adjacent sclera.
Conclusions and Importance: This case highlights the fact that regressed uveal melanomas can contain intratumoral bacteria.

1. Introduction

Microorganisms have a complicated relationship with cancer. Microbial infections have been noted not only to be drivers of carcinogenesis,[1,2] but have also been implicated in exceptional therapeutic responses.[3,4]

The impact of the intestinal microbiota on tumor biology, including processes like tumor transformation, progression, and response to various therapies, has been established and described in various neoplasms, particularly cutaneous melanoma and lung carcinoma.[5–8] The exact mechanisms by which bacteria or bacterial components can modulate cancer growth and/or therapy have not been fully elucidated.[6] It is hypothesized that the disorganized and permeable vasculature may allow circulating bacteria to enter and colonize the neoplastic tissue.[9,10] A recent comprehensive analysis of the tumor microbiome across different cancer types, found that each tumor type has a distinct microbiome composition, associated with a specific metabolic function and specific clinical features.[11] To our knowledge, there have been no prior peer-reviewed studies focusing on the role of the microbiome in uveal melanoma. Herein, we report a unique case of a patient with uveal melanoma, treated with plaque brachytherapy. Three years after treatment, histopathology of the blind and painful enucleated eye disclosed numerous bacteria within the residual tumor.

2. Case report

A 54-year-old white female with a past medical history of hypothyroidism and autoimmune hepatitis, previously treated with azathioprine, was referred to the Ocular Oncology Service at Wills Eye Hospital for evaluation of a ciliary body tumor in her right eye. Visual acuity was 20/30 in the right eye and 20/20 in the left eye. Examination of the right eye revealed an inferotemporal acoustically hollow, variably pigmented ciliochoroidal mass, measuring 18 × 16 mm in basal diameter and 15 mm in apical height, compatible with a large ciliochoroidal melanoma (Fig. 1). There was no evidence of extraocular extension. The left eye was unremarkable.

Both enucleation and plaque brachytherapy were discussed with the patient and she chose to have radiotherapy. The large tumor required a high dose of radiation. Iodine 125 plaque brachytherapy (22 mm round full plaque with radiation doses of 7000 cGy to the tumour apex, 71000 cGy to the tumour base, 5200 cGy to the optic disc, 6500 cGy to macula and 13900 cGy to the lens) was applied. Due to the significant risk for intraocular ischemia[12–15] and scleral necrosis,[16–18] intravitreal bevacizumab and a prophylactic scleral patch graft were performed at the

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time of plaque removal. Fine needle aspiration biopsy for molecular genetic studies performed at the time of plaque radiotherapy, disclosed disomy 3, disomy 6, disomy 8 (TCGA class A) and a *GNAQ* gene mutation.

The response to plaque brachytherapy was excellent: the tumor regressed from 15 to 7.5 mm in thickness. However, three years following treatment, the patient had developed chronic ocular ischemia with inflammation and radiation maculopathy that reduced her visual acuity to hand movements. There was no evidence of radiation-induced scleritis, conjunctivitis or uveitis. The patient initially responded to intraocular corticosteroids and topical antibiotics, but her eye became blind and painful and was enucleated four years after the plaque brachytherapy.

Histopathologic evaluation of the globe showed a heavily pigmented and extensively necrotic mushroom-shaped, regressed ciliochoroidal melanoma that was 7.5 mm in thickness. During initial assessment, large colonies of Gram-positive cocci were observed in the interface between the scleral patch graft and the underlying sclera (Fig. 3). These bacteria had not incited an acute inflammatory response, reminiscent of the pattern seen in infectious pseudocrystalline keratopathy. The tissue Gram stain used to assess the bacteria beneath the scleral patch graft disclosed large basophilic foci within the necrotic tumor that contained numerous Gram-positive cocci that occurred singly and in short chains (Fig. 2). Similarly, these bacteria had not incited an acute inflammatory response. No apparent communication between the bacteria in the episcleral cleft and the tumor was noted.

3. Discussion

We report the unusual observation of bacteria within an extensively necrotic ciliochoroidal melanoma following high dose plaque brachytherapy with a prophylactic scleral patch graft. The authors have not observed bacteria within a uveal melanoma previously.

The patient subsequently received sub-Tenon's and intraocular corticosteroid injections and intraocular anti-VEGF therapy for radiation complications. The exact mechanism by which the bacteria colonized the tumor in the patient is not entirely clear. The presence of the bacterial colonies underneath the patch graft suggests that the bacteria within the eye represent a secondary exogenous infection that entered the necrotic tumor through a sclera weakened by radiation-induced necrosis. Endogenous seeding via the circulation, as has been documented in prior studies[11] is considered unlikely. Blood cultures were not performed, but the patient showed no sign of a systemic infection. The patient's history of intraocular and peri-ocular steroid injections and immunosuppressive therapy for autoimmune hepatitis might be additional factors contributing to invasion.

Prior studies have demonstrated that interactions between bacteria, cancer cells, and the surrounding microenvironment can induce changes in tumor-infiltrating immune cells, cytokines and chemokines that can contribute to tumor regression.[19–21] or formation. The importance of immune microenvironmental modulation by microorganisms has been well-documented in cutaneous melanoma, but not in uveal melanoma.[20] Kalaora et al. analyzed the intratumour microbiota and the HLA peptides derived from these bacteria in metastases from 17 cutaneous melanoma and showed that the bacteria that colonize cutaneous melanoma can enter melanoma cells, and that their peptides can be presented by the tumor's HLA-I and HLA-II molecules. The latter play a central role in T cell immunity, the modulation of immune function and the survival and response of cancer patients to therapy.[20] Another study demonstrated that vancomycin-sensitive bacteria can promote tumor formation in a murine model of colitis-associated colon cancer.[22,23] Prior research has revealed that bacterial strains have various methods of tumor suppression in different types of nonocular tumors.[19] Salmonella species, for example, kill tumor cells directly by inducing apoptosis and/or autophagy via a variety of mechanisms.[19,24,25] Listeria species also can kill tumor cells directly via activation of nicotinamide adenine dinucleotide phosphate oxidase and increased intracellular calcium.[19,26] Clostridium species can release bacterial toxins that can disrupt the structure of cellular membranes.[19,27] The bacteria in our tumor were Gram-positive cocci that were not identified by culture.

Extensive necrosis of uveal melanomas and overlying sclera frequently develop when large tumors are treated with high doses of radiation. Therefore, we believe that the necrosis in our patient's tumor was caused by plaque brachytherapy. Although we cannot entirely exclude the possibility, we doubt that intratumoral bacteria contributed to tumor necrosis.

4. Conclusion

Although the mechanism of bacterial colonization in the case reported here is unusual and probably case-specific, the observation of bacteria within a uveal melanoma serves to draw our attention to studies that have shown colonization of tumors including melanomas at other sites. It may be worthwhile to evaluate other intraocular melanomas for this phenomenon, similar to what has been done for non-ocular melanoma. In that case, therapies targeting intratumoral microbiome may become relevant to intraocular melanoma.

Patient consent

Consent to publish personal information and case details has been obtained from the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for

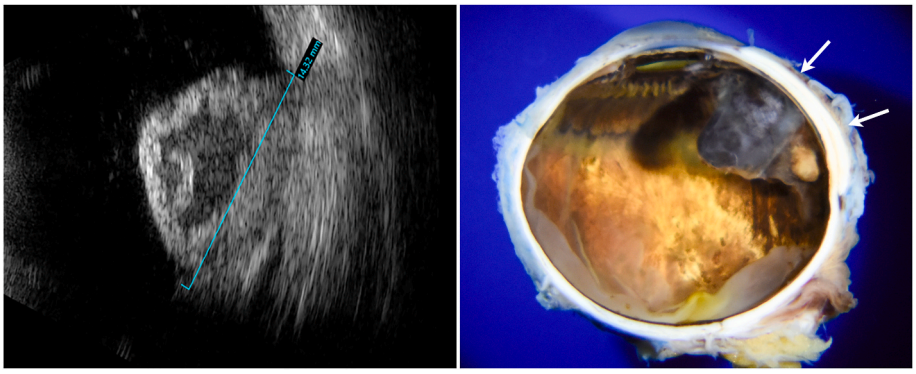

Fig. 1. 1A. B-scan ultrasonography discloses a dome-shaped mass with echolucency following plaque radiotherapy. 1B. Macrophoto of enucleated eye shows heavily pigmented mushroom-shaped ciliochoroidal tumor deep to scleral patch graft, which focally thickens the sclera (arrows).

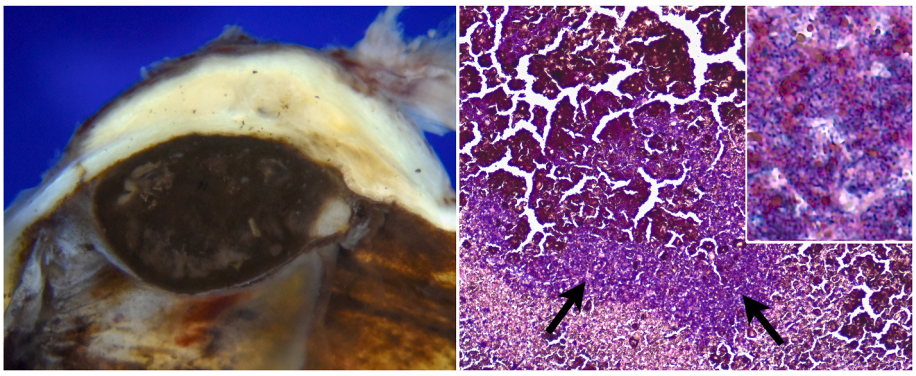

Fig. 2. 2A. Scleral patch graft markedly thickens sclera overlying intensely pigmented regressed melanoma. 2B. The presence of myriad bacteria causes basophilic areas (arrows) within the totally necrotic tumor. Gram-positive cocci are visible in the inset. 2A. Gram stain x50, inset x600.

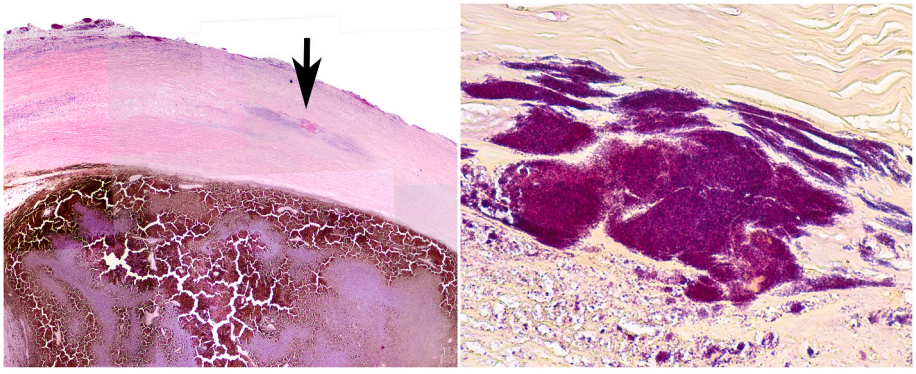

Fig. 3. 3A. Arrow denotes bacterial colony and necrotic debris in cleft between sclera and patch graft overlying necrotic melanoma. 3B. Large colony of Gram positive cocci in cleft shows no associated acute inflammation. 3A. Gram stain x10, 3B. Gram stain x150.

Authorship.

Acknowledgments and disclosures

No conflicting relationships exist for either author.

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