Simultaneous presentation of multifocal episcleral nodules and widespread systemic metastases following plaque radiotherapy of large choroidal melanoma

Despite efforts toward early diagnosis and prompt primary tumour treatment, metastases develop in approximately 50% of patients with uveal melanoma, the most common site of spread being the liver followed by the lungs and bones.[1] Because of the lack of intraocular lymphatics, uveal melanoma disseminates hematogenously unless there is scleral perforation or infiltration of the emissary canals and conjunctival lymphatics.[2] Local tumour extension is uncommon and typically involves the orbit.[3]

A 60-year-old female was referred for left eye choroidal melanoma. Visual acuity was 20/20 in both eyes. The anterior segment was unremarkable in both eyes with no melanocytosis. Fundus examination of left eye revealed a large choroidal melanoma inferiorly measuring 18 × 14 × 5.5 mm on B-scan ultrasonography with overlying orange pigment and serous retinal detachment (Fig. 1A). B-scan ultrasonography showed acoustic hollowness (Fig. 1B) with low internal reflectivity by A-scan, and there was no extraocular extension or ciliary body involvement. Staging liver function tests, chest computed tomography (CT), and abdominal CT showed no evidence of metastatic disease. The patient elected to undergo treatment with plaque radiotherapy and declined biopsy for prognostication. Iodine 125 plaque radiotherapy with a 22 mm round plaque and dose of 85 Gy to a depth of 6 mm was uncomplicated. There was no evidence of extraocular extension (EOE) at the time of plaque placement, and the sclera remained intact with uncomplicated muscle reinsertion at the time of plaque removal 94 hours later. The tumour showed the expected early response to radiation, shrinking to 5.1 mm in thickness at 2 months postoperatively, 4.6 mm at 4 months postoperatively with improved subretinal fluid, and 4.3 mm at 14 months postoperatively with resolved subretinal fluid (Fig. 1C, D).

However, at the 4-month postoperative visit, a new 1 × 1 mm flat episcleral pigmented lesion was noted near the 9:00 limbus on the left eye in an area not contiguous with the underlying choroidal melanoma (Fig. 2A). After discussion with the patient, the decision was made for short-interval observation of the episcleral lesion. Ten months postoperatively, the choroidal melanoma had regressed to 4.3 mm in thickness with complete resolution of subretinal

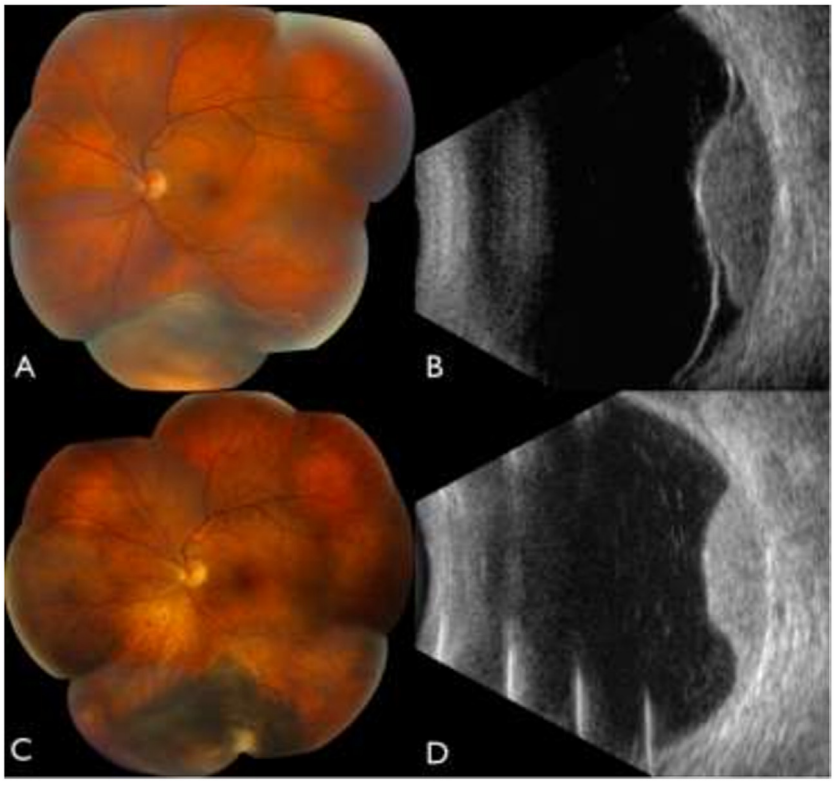

Fig. 1—Choroidal melanoma treated with plaque radiotherapy. A 60-year-old female presented with (A) choroidal melanoma located inferiorly measuring 18 × 14 × 5.5 mm with associated exudative retinal detachment and (B) acoustic hollowness on B-scan ultrasonography. (C) At 14-months follow-up after plaque radiotherapy, the subretinal fluid had resolved with tumour regression down to (D) a thickness of 4.3 mm.

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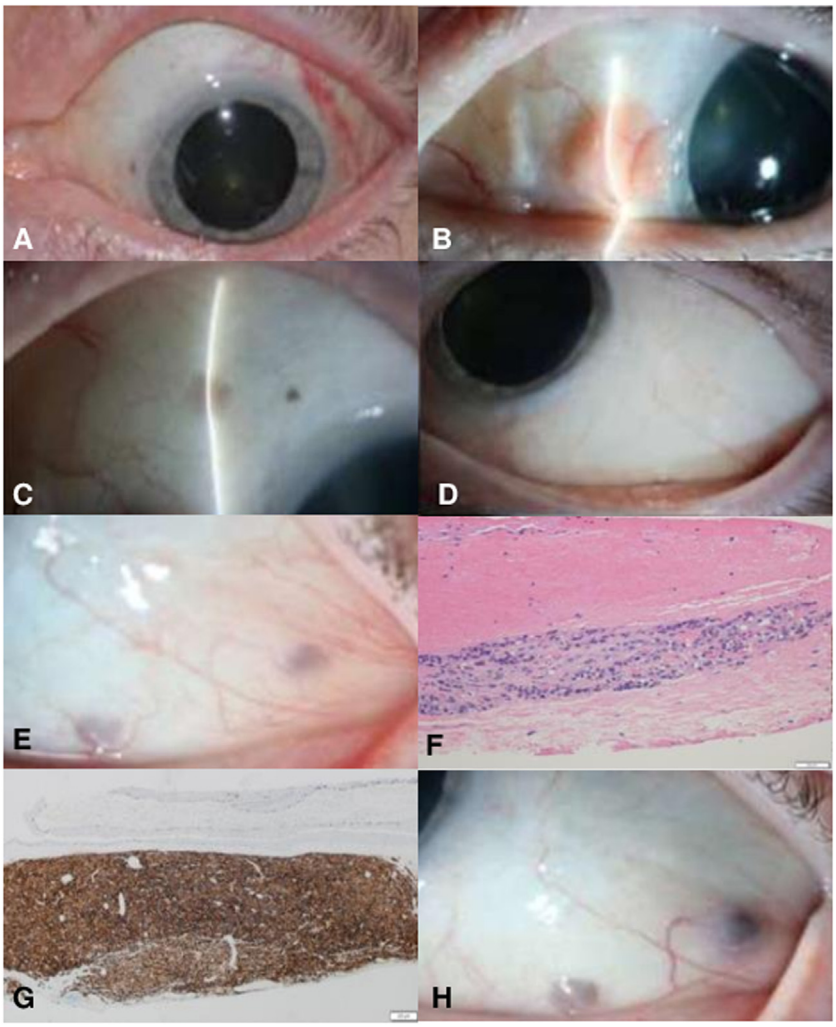

Fig. 2—Episcleral melanoma after uncomplicated plaque radiotherapy for choroidal melanoma. Choroidal melanoma with no ciliary body involvement or extraocular extension in the inferior quadrant was treated with plaque radiotherapy, at which time no conjunctival or episcleral lesions were noted. (A) Four months after plaque radiotherapy, a small pigmented episcleral lesion was noted at the 9:00 limbus, noncontiguous with the underlying area of choroidal tumour involvement. (B) At 10-months follow-up, an elevated amelanotic nodule was noted with (C) 2 additional pigmented episcleral lesions located superiorly. (D) At that time, there were no lesions located inferiorly in the region of the treated choroidal melanoma. (E) At 11-months follow-up, 2 pigmented episcleral lesions were noted inferotemporally. (F) Microscopic images of the episcleral biopsy show a cluster of malignant-appearing cells characterized by enlarged nuclei with prominent nucleoli. Intracytoplasmic melanin pigment is observed in some cells (hematoxylin & eosin stain; original magnification × 200). (G) Melanin immunostaining highlights a subconjunctival/intrascleral melanoma nodule (original magnification × 100). (H) Continued growth of lesions at 14 months despite systemic chemotherapy for widespread metastatic disease.

fluid, but the nasal area of flat episcleral pigment had progressed to a raised amelanotic nodule measuring 8 × 6 × 3 mm with 2 new, smaller foci of scattered episcleral pigment superiorly and faint pigment speckling near the 6:30–9:00 limbus (Fig. 2B, C). No nodules or areas of pigment speckling were in a contiguous location with the underlying choroidal tumour (Fig. 2D). Updated staging chest CT showed numerous new solid pulmonary nodules, the largest one measuring 12 × 9 mm. Abdominal magnetic resonance imaging showed innumerable hepatic masses. At 11-months follow-up (1 month after episcleral biopsy), 2 new episcleral pigmented lesions were noted inferotemporally (Fig. 2E). No orbital or intracranial involvement was seen by magnetic resonance imaging. Biopsies of the episcleral lesions (Fig. 2F, G), lung, and liver were all consistent with involvement by the patient's known primary uveal melanoma.

The patient was referred to medical oncology and was started on nivolumab 480 mg every 4 weeks. Two months after starting immunotherapy, bone scan showed metastatic lytic lesions in the occipital and left zygomatic bones. At follow-up 14 months after plaque radiotherapy, the choroidal tumour continued to regress, with slow growth of the inferotemporal episcleral pigmented lesions and progression of systemic metastases despite systemic treatment (Fig. 2H). There was no clinically evident extraocular extension of the choroidal melanoma on examination or imaging, with no scleral thinning and no radiation maculopathy. Despite

systemic treatment, the patient died of metastatic disease 29 months after primary tumour treatment.

While systemic metastases are a known sequela of uveal melanoma, simultaneous presentation with ipsilateral multifocal episcleral nodules after uncomplicated plaque radiotherapy without primary tumour biopsy is a novel finding. An iatrogenic etiology must be carefully considered, but suspicion was low in the absence of a surgical biopsy, no evidence ocular perforation during routine plaque placement and removal, and discrete metastases forming in scattered areas noncontiguous with the underlying tumour and even underlying a superior conjunctiva that was undisrupted during surgery. Perforation from scleral passes is associated with characteristic markings on the choroid on fundus examination, choroidal hemorrhage, vitreous hemorrhage, and draining vitreous or subretinal fluid. None of these findings were present in this patient with aggressive episcleral involvement and systemic metastases. The superficial ocular tumours were not located at suture sites, and there was no evidence of orbital involvement.

Uveal melanoma involvement of the conjunctiva, episclera, or sclera is rare, with only isolated reports in the literature. In a series of 2135 patients with choroidal melanoma from 1974 to 1986, 3 patients had orbital recurrence at 12, 18, and 84 months after primary enucleation, but none of the 123 patients (5.8%) with EOE had reported episcleral metastasis or recurrence.[3] In a series of 13,000 uveal melanoma patients in a study investigating the incidence of metastasis to contralateral eye structures, only 1 case of a conjunctival nodule with concurrent eyelid involvement was reposted.[4] A possible explanation for the episcleral nodules in our patient is microscopic involvement of the emissary canals without clinically detectable EOE, as reported by Dithmar et al.[2] in a case of lymphatic recurrence after enucleation in a patient who presented with choroidal melanoma extending to the ciliary body and iris with an anterior episcleral nodule.

Our patient did not have a primary tumour biopsy or overt EOE, either of which would have been a risk factor for local tumour spread. Based on careful review of the surgery and postoperative course, the episcleral nodules were inconsistent with an iatrogenic etiology and most likely due to clinically undetectable microscopic emissary canal invasion. Although our patient had expected regression of her primary tumour after plaque radiotherapy, multiple episcleral nodules with simultaneous systemic metastases developed and continued to progress despite systemic treatment. Multifocal ipsilateral episcleral nodular involvement in irradiated choroidal melanoma may indicate microscopic emissary canal invasion and aggressive disease. This case highlights an unusual presentation of rapidly progressive metastatic choroidal melanoma.

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Footnotes and Disclosure

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