BAP1 Germline Mutation Associated with Bilateral Primary Uveal Melanoma

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Established Facts

- Mutation in BRCA-associated protein 1 (*BAP1*) is strongly associated with hereditary uveal melanoma and other systemic malignancies.
- However, no genes to date have been implicated in the pathogenesis of bilateral uveal melanoma.

Novel Insights

- Two cases of patients with bilateral uveal melanoma and germline *BAP1* mutation suggest *BAP1* could contribute to the pathogenesis of bilateral uveal melanoma.

Keywords

Uvea · Bilateral melanoma · *BAP1* · BRCA-associated protein 1

Abstract

Purpose: To describe the occurrence of bilateral primary uveal melanoma in 2 patients with mutation on the gene encoding BRCA1-associated protein 1 (*BAP1*). **Methods:** Retrospective chart review of patients with bilateral primary uveal melanoma and subsequent positive germline *BAP1* mutation. **Results:** There were 2 patients with bilateral uveal melanoma and *BAP1* germline positivity. Neither patient demonstrated oculodermal melanocytosis. Patient 1 underwent enucleation of his right eye (OD) at the age of 44 years for a 9.6-mm-thick choroidal melanoma. He returned 4 years later with a 10.0-mm-thick choroidal melanoma in his left

eye (OS) and was treated with plaque radiotherapy. He had a strong family history of cancer, and clinical testing for germline *BAP1* mutation identified a pathogenic mutation in *BAP1*. At the 18-month follow-up, visual acuity was 20/200 OS without evidence of systemic metastasis. Patient 2 initially presented at age 54 years with extensive, diffuse iris melanoma OD, initially treated with plaque radiotherapy, but local recurrence after 3 years necessitated enucleation. Four years later, a 6.0-mm-thick ciliary body melanoma OS was found and successfully treated with plaque radiotherapy. Clinical testing for germline *BAP1* mutation identified a pathogenic mutation in *BAP1*. At the 8-year follow-up, visual acuity was 20/40 OS without evidence of local recurrence or systemic metastasis. The patient expired secondary to an unrelated brain infarction. **Conclusion:** Bilateral uveal melanoma is exceedingly rare. Patients with bilateral uveal melanoma, especially when coincident with remote systemic

cancers or a family history of cancer, should be evaluated for germline *BAP1* mutation. Lifelong monitoring for related systemic malignancies is advised.

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Introduction

Uveal melanoma is principally a unifocal and unilateral intraocular tumor [1], with rare reports of multifocal melanoma arising in one eye [2] or both eyes [3–9]. The first bilateral uveal melanoma was published in 1959 by Wiesinger et al. [3], who described a 32-year-old woman with a family history of leukemia and bilateral uveal melanoma. The patient finally expired secondary to leukemia. Later, in 1977, the second recording of bilateral uveal melanoma was published by Shammas and Watzke [4], who described a 55-year-old woman with sequential development of bilateral primary choroidal melanoma over 4 years. Using the lifetime risk of unilateral uveal melanoma and assuming a purely stochastic incidence of melanoma, Shammas and Watzke extrapolated the incidence of bilateral melanoma, estimating it to occur once every 18 years in the USA, at a rate of 1 in every 50 million Caucasians [4].

A subsequent study from our department in 1996 revealed 8 cases of bilateral uveal melanoma in a cohort of 4,500 patients at Wills Eye Hospital [5]. At 0.18%, this bilaterality rate was significantly higher than that reported by Shammas and Watzke [4]. Of the 8 cases, 2 (25%) displayed bilateral oculodermal melanocytosis, an established predisposing condition for bilateral uveal melanoma. The remaining 6 (75%) cases, however, showed no melanocytosis, suggesting the possibility of an underlying cancer predisposition syndrome [5].

Recently, sequencing of highly metastatic uveal melanomas has identified an associated inactivating mutation on the gene encoding BRCA1-associated protein 1 (*BAP1*) [2, 10–14]. These findings implicate loss of *BAP1* in uveal melanoma and suggest that there might, indeed, be more factors responsible for the bilaterality of uveal melanoma than chance alone. Herein, we report 2 cases of multifocal and bilateral uveal melanoma in which laboratory evaluation ultimately revealed germline *BAP1* mutation.

Case 1

A 48-year-old Caucasian man was referred for a ciliary body melanoma in the left eye (OS). Four years prior, his right eye (OD) was enucleated elsewhere for multifocal uveal melanoma. Histo-

pathologic examination of the enucleated globe OD revealed 2 noncontiguous class 1A mixed cell melanomas by gene expression profile testing. Clinical examination OS at the time was reportedly unremarkable. The patient was otherwise systemically healthy, with no history of cutaneous melanoma, immunosuppression, or presumed systemic malignancy. Family history was significant for ovarian and bladder cancer in his mother and pancreatic cancer in his maternal great grandfather.

On our examination, the anophthalmic right socket was healthy without evidence of tumor recurrence (Fig. 1a). Visual acuity OS was 20/40, with intraocular pressure of 13 mm Hg and no evidence of ocular melanocytosis. Slit-lamp examination revealed a new left eye ciliary body lesion (Fig. 1b). Funduscopically, there was a pigmented iridociliochoroidal melanoma inferonasal to the optic disc measuring 16.0 × 16.0 mm at base. B-scan ultrasonography showed a cavitory mushroom-shaped melanoma measuring 10.2 mm in thickness (Fig. 1c). Iodine-125 plaque radiotherapy was recommended. Cytogenetic profile of the tumor revealed disomy of chromosomes 3, 6, and 8. Germline genetic testing in a clinical laboratory identified a pathogenic frameshift mutation in *BAP1*, c.1717delC.

On follow-up 18 months later, tumor regression to 4.0-mm thickness was documented. There was no evidence of systemic metastasis.

Case 2

A 54-year-old Caucasian man was found to have an enlarging iris lesion OD with secondary glaucoma, refractory to topical medication. On referral, visual acuity was 20/30 OD and 20/20 OS, with intraocular pressure of 30 mm Hg OD and 14 mm Hg OS. There was no evidence of ocular melanocytosis. Examination of the left eye was normal. Slit-lamp examination of OD revealed a flat pigmented iris melanoma measuring 4.0 × 4.0 × 2.5 mm in diameter between 3:00 and 6:00 and satellite lesions at 7:00, 8:00, 9:00, and 10:00 (Fig. 2a). Gonioscopy showed 360 degrees of dense pigmentation within the angle. Three years after treatment with Iodine-125 plaque radiotherapy, local tumor recurrence led to enucleation. Histopathology confirmed epithelioid cell melanoma.

Four years after enucleation, the left eye was discovered to have a ciliary body melanoma of 10 mm in diameter (Fig. 2b) and 6.0 mm in thickness by ultrasonography (Fig. 2c). Cytogenetic profile revealed chromosome 3 monosomy, chromosome 6 disomy, and chromosome 8q amplification. Sequence analysis of the *BAP1* gene revealed a known pathogenic frameshift mutation, c.79delG, in exon 3. On follow-up 8 years later, tumor regression to 1.3-mm thickness was documented. There was no evidence of systemic metastasis. The patient died the following year from a cerebrovascular infarction.

Discussion

When Shammas and Watzke [4] first extrapolated the incidence of bilateral melanoma in their population-based study, the occurrence of bilateral primary uveal

Fig. 1. Case 1: bilateral primary uveal melanoma in *BAP1* germline mutation. **a** The anophthalmic socket OD following enucleation (elsewhere) for multifocal melanoma. **b** Four years later, slit-lamp

examination revealed a new ciliary body lesion in the left eye. **c** Ultrasonography OS revealed a cavitary mushroom-shaped ciliary body melanoma.

Fig. 2. Case 2: bilateral primary uveal melanoma in *BAP1* germline mutation. **a** Slit-lamp examination OD showed diffuse iris melanoma with heavy-angle pigmentary seeding and minor hyphema. This eye was treated with plaque radiotherapy and later enucle-

ation. **b** Seven years following enucleation, a new ciliary body lesion was discovered in the left eye. **c** Ultrasonography of the lesion OS showed a dome-shaped ciliary body mass.

melanoma was thought to be a rare, random event, with odds deducible by statistics alone [3–9]. However, three subsequent independent reviews of patients with uveal melanoma have reported consistently higher rates of bilateral primary uveal melanoma, equating to 1.5–2 per 1,000 cases (0.15–0.20%) of unilateral primary uveal melanoma [5, 14, 15]. These clinic-based reviews might more accurately reflect the true incidence of bilateral primary uveal melanoma. Compared to a cross-sectional, population-based study, referral center-based reviews are better equipped to capture rare cases of bilaterality. The ability to examine follow-up data also increases the chance of identifying cases of sequential involvement of the contralateral eye, which are seen more often than those with simultaneous involvement of both eyes. In one systematic review of 52 cases of bilateral uveal mela-

noma [6], most (69%) of the bilateral cases presented initially as unilateral tumors, with sequential bilateral involvement occurring between 22 months [5] and 10 years [6] later.

The discrepancy between the observed and the expected incidence of bilateral melanoma might indicate the presence of predisposing factors to bilateral tumors. Environmental factors, such as arc welding and immunosuppression, have been proposed [7, 16]. Bilateral oculo(dermal) melanocytosis has been identified as a possible risk factor for bilateral uveal melanoma [17, 18], with pre-existing ocular melanocytosis described in 12–25% of bilateral uveal melanoma patients [5, 6].

The bilaterality of a primary cancer in a paired organ, however, has always been highly suggestive of an inherited cancer predisposition [19]. The most preva-

lent examples include hereditary bilateral breast carcinoma in patients with germline BRCA1 and BRCA2 mutation [19, 20], bilateral renal cell carcinoma and retinal hemangioblastoma in von Hippel-Lindau (VHL) syndrome with germline VHL mutation [21], and bilateral retinoblastoma (RB) in patients with germline RB1 mutation [1]. Such observations, coupled with the discrepancy between the observed and expected frequencies of bilateral primary uveal melanoma, have led many to speculate a genetic predisposition [5, 6].

Although no genes have been implicated in the pathogenesis of bilateral uveal melanoma, *BAP1* has been identified as a high-penetrance gene for hereditary uveal melanoma (familial uveal melanoma) [11]. Mutation of this gene follows an autosomal dominant inheritance pattern and causes a spectrum of systemic malignancies (*BAP1* tumor predisposition syndrome) [11, 12]. An analysis of 174 cases of patients with germline *BAP1* mutation showed preponderance for uveal melanoma (31%), followed by malignant mesothelioma (22%), atypical Spitz tumor (18%), cutaneous melanoma (13%), renal cell carcinoma (10%), and others [12]. The risk for developing uveal melanoma in the presence of *BAP1* germline mutation is estimated at up to 29% [12], and it is associated with class 2 uveal melanoma tumors and poor survival [11]. Subsequent publications have reported *BAP1* germline mutation in patients with familial uveal melanoma [14], multifocal uveal melanoma in a single eye [2], and growth of nevus to melanoma in a predisposed patient [22].

Based on our experience and reports in the literature, we propose a simple “rule of twos” to serve as a guideline for considering *BAP1* testing. We propose *BAP1* testing should be performed in patients with (i) two or more *BAP1*-related cancers (particularly uveal melanoma, cutaneous melanoma, renal cell carcinoma, or malignant mesothelioma) in a single patient, (ii) two or more suspected primary sites of uveal melanoma in one eye (multifocal) [2] or both eyes (bilateral), or (iii) two or more family members (first or second-degree relatives) with *BAP1*-related cancers [12]. An early age of onset of any *BAP1*-associated tumors should also warrant consideration for *BAP1* testing [13].

Both patients in our series presented with ciliary body melanoma in the contralateral eye, a finding described by Gupta et al. [23] in a comparative study on 507 patients with uveal melanoma, in which 1.6% demonstrated a pathogenic germline *BAP1* mutation. The study showed a preponderance for ciliary body involvement in

patients with *BAP1* mutation compared to those without (75 vs. 22%, $p = 0.002$). Furthermore, risk for metastasis was significantly greater with *BAP1* germline mutation (71 vs. 18%, $p = 0.003$), although neither of our 2 patients has shown metastatic disease on early follow-up.

Theoretically, bilateral uveal melanoma could result from metastases of a primary tumor to the contralateral eye or from a nonocular primary site (e.g., cutaneous melanoma) to one or both eyes. In our series, however, a full systemic workup revealed neither extraocular metastasis nor nonocular melanoma in either patient. Thus, both cases likely represent true cases of primary bilateral disease. To the best of our knowledge, this is the first report of bilateral uveal melanoma in patients with germline *BAP1* mutation, following the prediction made in our publication from 1996 regarding a yet unidentified inherited genetic predisposition for bilateral uveal melanoma [5].

Of note, the mutation identified in patient 1, c.1717delC, is a founder mutation originally described by Carbone et al. [24] and since reported by others as well [13, 25]. In our patient, this mutation was uniquely associated with two uveal melanomas that were class 1 and disomy 3, which is unusual in germline *BAP1* pathogenic mutations. It is plausible that biallelic inactivation of *BAP1* resulted from mutation or epigenetic inactivation.

In summary, we describe a rare entity of sequentially bilateral primary uveal melanoma in 2 patients with germline *BAP1* mutation. In patients with positive *BAP1* mutation, the possibility of bilateral disease should be considered when deciding enucleation versus conservative treatment. Close monitoring for related systemic cancers is advised.

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Statement of Ethics

The study protocol was exempted by the Wills Eye Hospital Institutional Review Board. The study was conducted in accordance with the tenets of the Declaration of Helsinki or comparable ethical standards. Patient consent was obtained for the publication of medical history and imaging.

Disclosure Statement

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