

A RARE PRESENTATION OF MULTIFOCAL CHOROIDAL MELANOMA



The multifocal lesions, themselves rare, were even more unexpected in the absence of ocular melanocytosis and germline *BAP-1* mutation.

BY ERIN JENNINGS, BS; MICHAEL CHANG, MD; AND CAROL L. SHIELDS, MD

Uveal melanoma is a rare tumor with an incidence of 4.3 per million people in the general population.¹ This malignancy is typically solitary and unilateral, rarely manifesting as multifocal unilateral or bilateral tumor.² In an analysis of 8,033 eyes with uveal melanoma by Shields et al, less than 1% of patients (11 of 8,022) presented with either multifocal or bilateral tumors.²

Predisposing factors associated with the development of uveal melanoma include preexisting choroidal nevus; ocular melanocytosis; breast cancer type 1 (*BRCA1*)–associated protein (*BAP-1*) cancer predisposition syndrome; and, rarely, neurofibromatosis and myotonic dystrophy.^{1,3-5}

Ocular melanocytosis, a congenital pigmentary abnormality, promotes a 1 in 400 risk for uveal melanoma (compared with 1 in 13,000 in the general white population).⁶ In a study of 507 patients with uveal melanoma who underwent germline *BAP-1* sequencing, Gupta et al identified 25 patients (4.9%) harboring an underlying *BAP-1* mutation, and this can promote multifocal melanoma.⁷

Here we report a unique case of multifocal uveal melanoma in a patient with no evidence of ocular

melanocytosis or *BAP-1* cancer predisposition syndrome.

CASE REPORT

A 56-year-old white woman with a history of two choroidal nevi in the right eye (OD) reported experiencing photopsia for 3 weeks. She related a family history of leukemia, prostate cancer, and breast cancer, but reported no previous personal history of cancer.

On our examination, VA was 20/25 OD and 20/20 in the left eye (OS). IOP was 13 mm Hg in each eye. On anterior segment examination, there was no ocular melanocytosis on either eye. However, two iris freckles were noted OS. Fundoscopic examination of the left eye was unre-

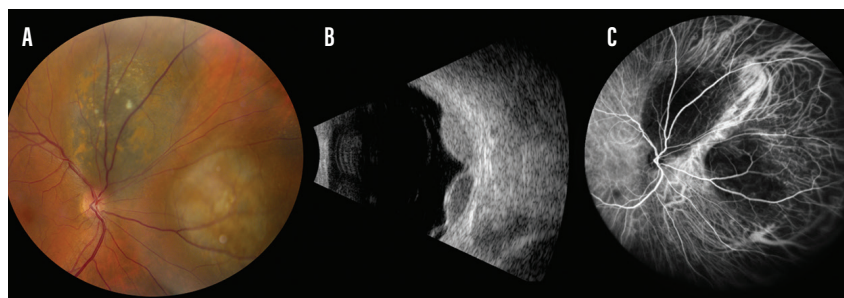


Figure. Multifocal choroidal melanoma in the right eye of a 56-year-old woman (A). B-scan ultrasonography showed two distinct hollow, dome-shaped lesions with subretinal fluid (B). Evaluation with indocyanine green angiography documented hypocyancence at the two tumor sites with normal choroidal flow in between, implying two distinct tumors (C).

markable. Funduscopy examination of the right eye showed two independent small choroidal melanomas located superonasal to the optic disc and nasal to the optic disc (Figure, A).

B-scan ultrasonography documented two distinct echolucent tumors, with No. 1 (superonasal) measuring 9.0 mm in base and 4.6 mm in thickness and No. 2 (nasal) measuring 9.0 mm in base and 4.3 mm in thickness (Figure, B). There was no extrascleral extension, and the two tumors were distinct.

Fluorescein angiography revealed patchy areas of hyperfluorescence in both tumors during the arteriovenous phase. Indocyanine green angiography displayed the tumors as hypocyanc-

cent and with no evident connection between the two independent melanomas (Figure, C). Autofluorescence revealed prominent orange pigmentation over both tumors.

OCT revealed macula-sparing subretinal fluid extending from 2 o'clock to 8 o'clock at the ora serrata in the right eye. Additional fluid was noted between the two tumors, and no connection between the two tumors was seen on OCT.

Fine needle aspiration biopsy for cytogenetic analysis was performed, and tumor No. 1 showed chromosome 3 monosomy, partial loss in chromosome 1, chromosome 6 disomy, and chromosome 8q gain and 8p loss, suggestive of high risk for metastasis and correlating with The Cancer Genome Atlas (TCGA) classification of group C.⁸ Cytogenetics of tumor No. 2 showed chromosome 3 partial monosomy as well as chromosomes 1, 6, and 8 disomy, suggestive of TCGA group A. The patient was negative for germline *BAP-1* mutation.

The melanomas were treated simultaneously with plaque radiotherapy using a single 22-mm notched radioactive iodine-125 device. At 24-month follow-up, both tumors demonstrated regression, with tumor No. 1 decreasing in thickness from 4.6 mm originally to 2.4 mm and tumor No. 2 from 4.3 mm originally to 2.1 mm. Systemic evaluation at 2 years confirmed absence of metastatic disease.

DISCUSSION

Multifocal melanoma is an extremely rare condition. Based on the reported risk of developing uveal melanoma in patients with ocular melanocytosis, Honavar et al estimated a lifetime risk of 1 in 160,000 for developing two uveal melanomas in the same eye.^{6,9}

From a genetic perspective, *BAP-1* is a recognized predisposing factor associated with multifocal uveal melanoma, but other gene mutations, some as yet unrecognized, could contribute to this condition.¹ Guanine nucleotide-binding protein G (*GNAQ/GNA11*) mutations, which are present in 85% of all uveal melanomas, are involved in regulation of the mitogen-activated protein kinase pathway; it has been speculated that this pathway is involved in the malignant transformation of melanocytes.¹⁰

Other genes, such as eukaryotic translation initiation factor 1A (*EIF1AX*), splicing factor 3B subunit 1 (*SF3B1*), and preferentially expressed antigen in melanoma (*PRAME*), have also been identified as having an influence on patient outcomes.¹ Several of these genes—*BAP-1*, *EIF1AX*, and *SF3B1*—have been found to be mutually exclusive of one another, illustrating the complexity involved in tumor development.¹⁰ There may be other as yet undiscovered germline or somatic mutations that contribute to the development of multifocal uveal melanoma.

The *BAP-1* gene, located on the short arm of chromosome 3, expresses a tumor-suppressor protein that works with a variety of recombination proteins (most notably *BRCA-1*) to enhance regulation of DNA repair, cell cycle mechanisms, cellular differentiation, and genomic sta-

bility.¹ Rao et al reported the first case of multifocal uveal melanoma with presence of germline *BAP-1* mutation, suggesting the importance of germline testing in uveal melanoma, especially in multifocal cases.⁴

In addition to uveal melanoma, patients with an autosomal dominant germline mutation of this gene are at risk for other heritable cancers described as *BAP-1* tumor predisposition syndrome (*BAP1-TPDS*).¹ In a review of the literature of 246 patients with underlying *BAP-1* mutation, Masoomian et al observed that 63% of patients (156 of 246) developed one or more tumors, including mesothelioma (20%), cutaneous melanoma (10%), renal cell carcinoma (8%), atypical Spitz tumor (AST), breast cancer, and prostate cancer, among others.¹

BAP-1 mutations have also been associated with a strong family history of cancer. Gupta et al studied 507 patients with uveal melanoma who underwent germline *BAP-1* sequencing.⁷ They found that those with germline *BAP-1* mutations (versus those without mutation) had a higher frequency of family history of any cancer (100% vs 65.9%, $P = .06$), family history of ocular melanoma (25.0% vs 1.9%, $P = .01$), and personal history of cutaneous melanoma (62.5% vs 9.9%, $P = .001$).⁷

Given an increased risk of systemic cancer in patients with *BAP1-TPDS*, Masoomian et al advised genetic testing of patients with early onset of uveal melanoma (< 30 years old) or one or more of the following: family history with two or more uveal melanoma cases, uveal melanoma with another primary neoplasm, two or more primary tumors in first- or second-degree relatives, and bilateral or multifocal tumors.¹

The presence of multiple lesions with a strong family history of cancer in this case raised suspicion for an underlying mutation, despite the patient's having no detectable pathologic *BAP-1* variants.

In addition to germline *BAP-1*, somatic *BAP-1* can be a prognostic biomarker for uveal melanoma metastasis. Located on chromosome 3p21.1, *BAP-1* is strongly correlated with monosomy 3.¹ However, tumor studies have expanded beyond single chromosome 3 analysis, now including chromosomes 1, 6, and 8, highlighting the polygenic influence on uveal melanoma prognosis.^{8,10}

Shields et al studied 1,059 patients with somatic genetic testing of uveal melanoma and identified the highest metastatic risk in those with complete monosomy 3 combined with disomy 6, 8q gain, and 8p loss (hazard ratio, 31.6).¹⁰

TCGA describes the genetic influence on uveal melanoma prognosis by categorizing tumors into four classes based on somatic karyotype: classes A (disomy 3, normal 8q), B (disomy 3, 8q gain), C (monosomy 3, 8q gain), and D (monosomy 3, multiple 8q gains). This system was examined by Vichitvejpaisal et al in a study of 658 patients, and these authors confirmed the reliability of the TCGA classification for prediction of metastasis and death.⁸ A comparison (class

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A vs B vs C vs D) revealed that more advanced classifications had increasing 5-year risk of metastasis (3% vs 10% vs 25% vs 41%, $P < 0.001$).⁸ This information highlights not only the utility of TCGA classification system, but also the influence that genetics has on tumor behavior.

CONCLUSION

Here we have presented a case of a patient with unilateral, multifocal uveal melanoma who lacked detectable mutation in *BAP-1* or presence of ocular melanocytosis. We speculate that there may be other as yet undiscovered germline or somatic mutations that could lead to multifocal uveal melanoma. ■

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