

The Relationship Between Cutaneous and Uveal Melanoma

These different entities share some similarities.

BY MIGUEL A. MATERIN, MD

Melanomas are malignant tumors that develop from pigmented cells called melanocytes. These cells are found in the skin, the eye, the mucosal epithelia, and other locations in the body. The skin is the most common site for development of melanoma, but these malignancies can occur in any tissue that contains melanocytes.¹

There has long been discussion of the relationship or relationships between cutaneous and ocular melanoma: Are they the same disease? How are they different? The two share some characteristics but differ in other important ways. With the emergence of genetic analytic technologies, clearer pictures of ocular and cutaneous melanoma have begun to appear. I recently coauthored an article with 2 colleagues at Yale, the surgical oncologist Mark Faries, MD, and the medical oncologist Harriet Kluger, MD, examining the molecular abnormalities in these two diseases. The article below recaps some of the information presented in that article and explores its implications for ophthalmic practice.

SIMILARITIES AND DIFFERENCES

Uveal melanoma is the most common primary intraocular malignancy in adults, with about 2000 new cases diagnosed in the United States each year.² By comparison, cutaneous melanoma is much more common, with more than 68 000 new cases diagnosed each year in the US population. While the incidence of cutaneous melanoma is increasing, the incidence of ocular melanoma has been stable for half a century.³ It has been estimated that 50% of patients with uveal melanoma die from metastatic disease, while the figure cited for cutaneous melanoma is 12%.

At the cellular level, cutaneous and uveal melanomas share the same lineage, but they differ in their etiologies, clinical features, and molecular abnormalities. Both malignancies originate from melanocytes and are seen more frequently in individuals with fair skin. The size of the tumor and its degree of invasion are prognostic in both entities. But the patterns of dissemination and metastasis differ between the two. Uveal melanoma spreads through the blood, while cutaneous melanoma can spread through both the blood and the lymphatic system. The most common site of metastasis of uveal melanoma—in more than 90% of cases of metastasis—is the liver. Cutaneous melanoma, on the other hand, can spread to other sites on the skin, as well as to the lymph nodes, lung, brain, and soft tissue.

MOLECULAR ABNORMALITIES

The differences in disease dissemination patterns between cutaneous and uveal melanoma probably reflect differences in tumor biology between the two entities. Researchers have begun to identify molecular characteristics of cutaneous melanoma that affect its clinical response to certain therapies. Two recent clinical trials have shown a survival benefit with molecular targeted therapies for cutaneous melanoma, one with the drug ipilimumab, which targets CTLA-4, and another with an inhibitor of the BRAF gene, for which there are activating mutations in approximately half of melanomas.

The search for molecular abnormalities in ocular melanoma is not as advanced as in the cutaneous disease. This is due in part to the lower incidence of the disease and to the lack of access to tissue samples from ocular melanomas. Often uveal tumors are not excised or are

too small to grow cultures for research purposes. In addition, metastasis is primarily to the liver, which is not easily accessible to biopsy.

Genetic abnormalities associated with uveal melanoma include chromosomal abnormalities, gene expression patterns, and genetic mutations. Certain protein biomarkers have also been found to be associated with uveal melanoma or its progression.

Chromosomal abnormalities. Since Sisley and colleagues⁴ described alterations in chromosomes 3, 6, and 8 in uveal melanomas, the significance of these associations has been further evaluated. Monosomy 3 has been found to be a strong predictor of metastasis. In a study including 356 patients with uveal melanoma, Damato et al⁵ found that almost all metastatic deaths occurred in patients with monosomy 3. More recently, studies using fine-needle aspiration biopsy (FNAB) for chromosome 3 analysis⁶ showed improved survival in patients with disomy 3 or partial monosomy 3 compared with those with monosomy 3. It is not clear whether these chromosome 3 abnormalities are indicative of worse tumor biology or are themselves responsible for changes in tumor suppressor genes that lead to worse outcomes.

Protein biomarkers. Investigators have noted the overexpression of certain mediators of tumor growth in uveal melanoma. The most familiar of these factors to ophthalmologists, vascular endothelial growth factor (VEGF), as well as CXCR4, was associated with tumor progression in 53 samples from primary uveal melanoma and liver metastases.⁷ Possible association of prognosis with the melanoma cell adhesion molecule (MCAM) gene was found in a study of 35 primary uveal melanomas.⁸ Other proteins that appear to be overexpressed or upregulated in uveal melanoma include HGF, c-Met, IGF-1R, EGF-1r, and iNOS.^{9,10}

The search for prognostic biomarkers that could represent possible drug targets in uveal melanoma is hindered by the relatively small quantities of tissue available for study. The papers cited here are all based on fewer than 100 specimens, while biomarker studies in cutaneous melanoma often include hundreds of cases, primary and metastatic. Larger studies are needed to improve the statistical power of biomarker identification and validation in uveal melanoma.

High-throughput profiling. High-throughput profiling technologies have begun to identify genetic aberrations in other cancers, such as breast cancer, that can provide clues to prognosis in early-stage malignancies. Similar efforts have been undertaken for uveal melanoma. Onken and colleagues¹¹ profiled 25 primary uveal melanomas and compared the expression profiles to

those of normal ocular melanocytes. They found 2 distinct tumor classes, one with a poor prognosis and one with improved prognosis. These results were validated in a larger cohort using polymerase chain reaction, in which tumors were classified as good or poor prognosis with a low rate of error.¹² Many of the differentiating genes were located on chromosomes 3 and 8. An assay being developed by Onken's group will be able to use specimens obtained by FNAB for analysis.

Gene expression profiles can also reveal details about tumor biology. Onken et al¹¹ used gene expression data to identify biologic characteristics of the aggressive, poor prognosis class of tumors and found a down-regulation of neural crest and melanocyte-specific genes and upregulation of epithelial genes in the more aggressive class of tumors. These tumors exhibited epithelioid features, such as polygonal cell morphology and upregulation of the epithelial adhesion molecule E-cadherin. The investigators identified E-cadherin as a possible target for therapeutic intervention in aggressive uveal melanoma.

Interestingly, this is an area of similarity between uveal and cutaneous melanoma; in both entities, cells in the more aggressive tumors have more epithelioid features.

Aneuploidy, an abnormal number of chromosomes, is a hallmark of cancer and is associated with metastasis and poor clinical outcome. Ehlers et al¹³ looked at patterns of aneuploidy and chromosomal alterations in choroidal melanoma using gene expression profiling and comparative genomic hybridization. They found that aneuploidy and changes in chromosomes 3 and 6p were associated with worse survival. In particular, PTEN, a tumor suppressor gene and genomic integrity guardian, was downregulated in association with increasing aneuploidy. Drugs that target the pathway in which PTEN is involved are in clinical development for cutaneous melanoma, and this work suggests that these drugs could have important clinical implications in uveal melanoma.

Genetic mutations. A number of somatic mutations have been described in uveal melanoma. Mutations in GNAQ and GNA11, genes that encode for the proteins GNAQ and GNA11, respectively, have been observed and subsequently validated. Van Raamsdonk and colleagues found mutations in GNAQ in 46% of 48 samples of uveal melanoma.¹⁴ No mutations in GNA11 were seen in that set of samples, but mutations in both GNAQ and GNA11 were seen in a larger set of specimens that included 186 uveal melanomas and 282 cutaneous or mucosal melanomas.¹⁵ In that study, 45% of primary and 22% of metastatic uveal melanomas had a mutation in GNAQ, and 32% of primary and 57% of metastatic melanomas had mutations in GNA11.

These mutations may have therapeutic implications,

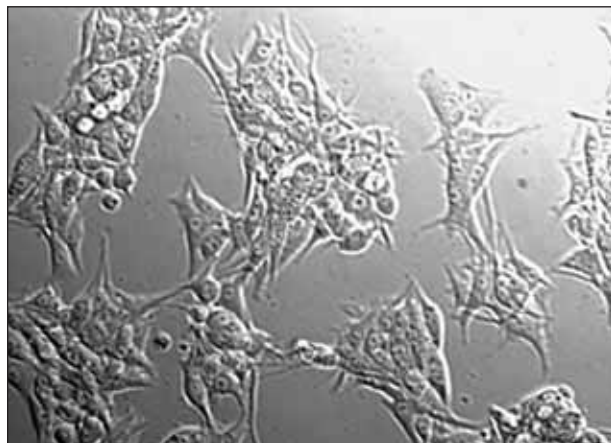


Figure 1. Uveal melanoma cell line for sequencing from enucleated eye.

as mouse studies suggest that GNAQ and GNA11 mutations may sensitize uveal melanoma cells to drugs that inhibit the MAPK pathway. Activation of the MAPK pathway has been seen in both cutaneous and uveal melanoma.

Next-generation sequencing has identified mutations in the BRCA1-associated protein 1 (BAP1) gene in poor prognosis uveal melanomas.¹⁶ Sequencing of the BAP1 gene in 29 tumors with poor prognosis and 26 with good prognosis found mutations leading to loss of protein expression in 84% of the tumors with poor prognosis and only 4% of those with good prognosis. Genes that are upregulated by loss of BAP1 might be potential targets for drug development for uveal melanoma.

Mutations in BRAF and NRAS have been described in cutaneous melanoma. For the most part, these mutations have not been seen in uveal melanoma, although BRAF mutations have been described in conjunctival and iris melanomas.

THERAPEUTIC IMPLICATIONS

As with the search for molecular abnormalities, progress in seeking and finding targeted therapies for uveal melanoma has been slow because of the relatively small numbers of cases and lack of access to tissue. Few clinical trials of targeted therapies have been conducted with a focus on uveal melanoma.

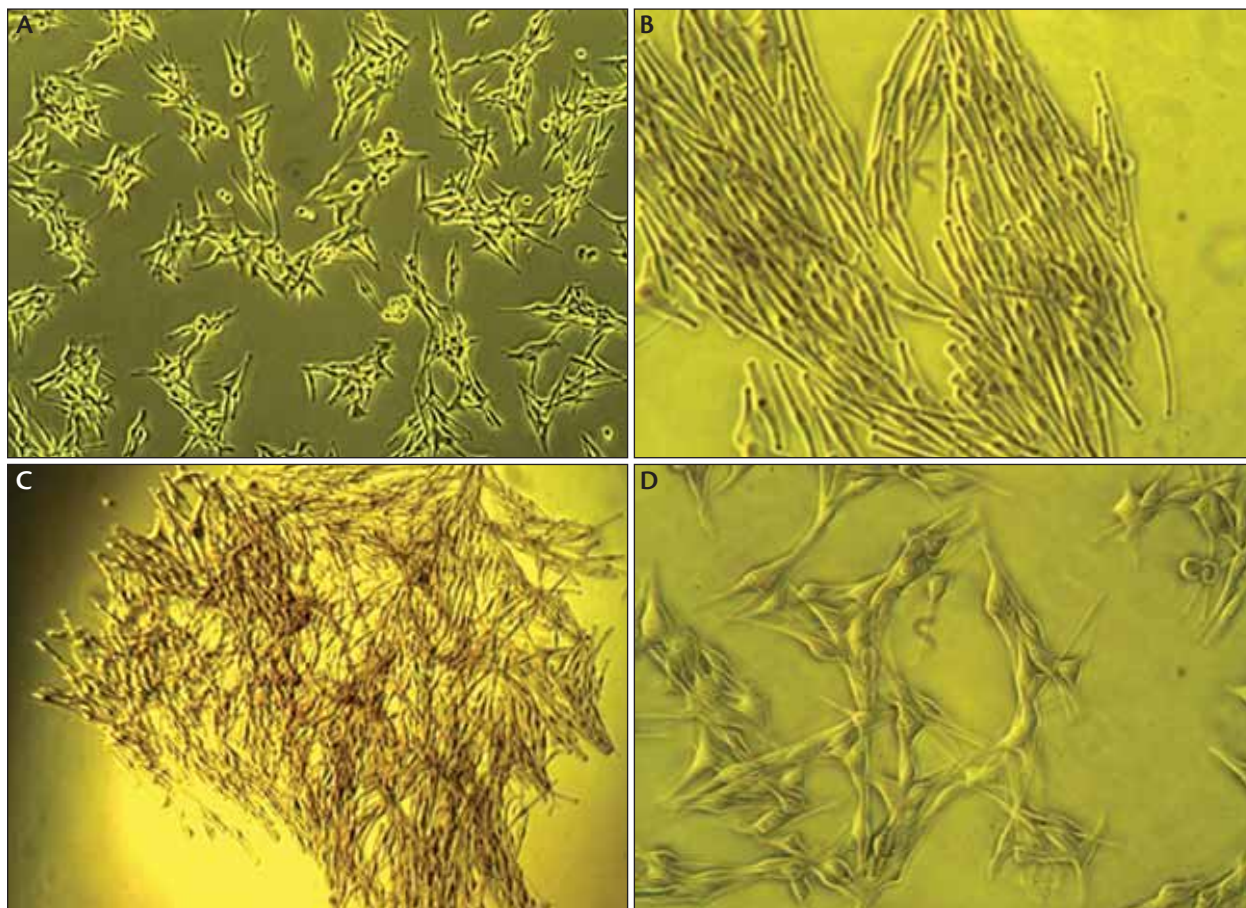


Figure 2. Choroidal melanoma cell line from fine-needle aspiration biopsy.

TABLE 1: ONGOING CLINICAL TRIALS WITH SYSTEMIC THERAPY SPECIFIC FOR PATIENTS WITH METASTATIC UVEAL MELANOMA

Drug	Target	Coadministered agents
Genasense	Bcl-2	Carboplatin and paclitaxel
Everolimus and pasireotide	mTOR and somatostatin receptors	Combination therapy
AZD6244	MEK	Single agent vs temozolamide
Abraxane	Microtubules	Single agent
Bevacizumab	VEGF	Combination with temozolamide
Liposomal vincristine	Microtubules	Single agent
Ipilimumab	CTLA-4	Single agent
Interferon alpha-2b	Interferon responsive genes	Dacarbazine

Clinical trial information was obtained from <http://www.clinicaltrials.gov>. This table does not include trials of systemic therapy open to patients with both uveal and cutaneous melanoma.

Adapted from Materin et al.²

Results with the tyrosine kinase inhibitor imatinib mesylate (Gleevec, Novartis) in uveal melanoma were disappointing, as overexpression of c-Kit in three-quarters of melanomas did not translate into clinical efficacy.¹⁷ Drugs are in development for a number of other possible targets in uveal melanoma, including mediators of angiogenesis such as VEGF.

The identification of targets specific to metastatic uveal melanoma and the initiation of clinical trials to address them is only just beginning. Drugs and drug candidates being evaluated in studies that are currently enrolling patients with high-risk uveal melanoma include oblimersen sodium (Genasense, Genta, Inc.), the MEK inhibitor selumetinib (Array Biopharma), and bevacizumab (Avastin, Genentech). Table 1 lists ongoing clinical trials of systemic therapy specific for patients with metastatic uveal melanoma. The table also includes trials assessing immunotherapy in metastatic uveal melanoma, which primarily capitalize on findings in cutaneous melanoma.

The advances seen in the treatment of cutaneous melanoma have yet to be replicated in uveal melanoma, although some promising potential targets have been identified. Most uveal melanomas are diagnosed clinically and treated with brachytherapy, and therefore tissue for molecular profiling does not become available in many cases. FNAB can be a useful source of tissue for genetic studies.

At our center, we are trying to sequence as many tissue samples from uveal melanoma patients as possible (Figures 1 and 2). Obviously some tumors are larger and yield tissue samples for sequencing more easily than others. We routinely perform FNAB on all uveal melanoma

patients to study the cytogenetics for prognosis. When there is enough tissue, we take a second biopsy to sequence the tumor.

We do not want to put patients at higher risk for eye complications only for the sake of research. I counsel every patient in detail about the implications of these investigations. Most patients are eager to contribute tissue for the sake of research. In the case of large melanomas, for which enucleation is the treatment, 100% of these patients agree to the use of their tissue. If possible, we take 3 specimens: 1 for cytogenetic analysis, 1 for sequencing, and a third for cytology. If an eye is enucleated, the globe is sent to pathology, and 2 specimens are taken: 1 for cytogenetic analysis and 1 for sequencing. We also take samples of blood for sequencing.

We are also referring patients for cancer genetic counseling when the patient is young (less than 20 years of age), when there is a strong personal or family history of cancer, or if there is a personal or family history of cutaneous melanoma.

If more academic centers would commit to gathering tissue samples routinely, the number of samples available for molecular profiling could be greatly expanded, perhaps leading to stronger identification of the molecular characteristics of uveal melanoma and the discovery of potential targets for therapy. Collaborative effort by physicians who treat uveal melanoma to share these tissues or the results of their investigations could lead to studies of larger cohorts with stronger statistical findings.

We are still in the learning stages with uveal melanoma, still exploring the significance of the molecular abnormali-

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ties that have been identified. For inspiration, we can look to the successes achieved in cutaneous melanoma, such as the regulatory approval earlier this year of the targeted therapy ipilimumab (Yervoy, Bristol-Myers Squibb) for treatment of advanced melanoma. We need to find specific drugs for specific mutations related to ocular melanoma, borrowing lessons from cutaneous melanoma and other cancers when possible. As potential therapies emerge, the concerted cooperation of ocular oncologists could lead to the design and execution of clinical trials and hopefully the identification of safe and efficacious treatments for this sight- and life-threatening malignancy. ■

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