inSight

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GENETIC IMPLICATIONS OF OCULAR MELANOMA

Gene expression profiling is increasingly used in many tumors like breast, colon and lung for prognostication and tailoring treatment for patients. Genetic anomalies in uveal melanoma were first reported in the 1990's and the genetic changes reported were monosomy 3, isochromosome 6p, trisomy 8, and isochromosome 8q. Various genetic and epigenetic alterations occur along the 'melanoblast–melanocyte–nevus–Uveal melanoma' pathway, resulting in malignant transformation and propensity to spread. A landmark paper in 1996 showed that patients with Monosomy 3 had significantly higher rates of metastasis ~ 50% at 5 years. Since then extensive research has been conducted to isolate multiple genetic markers in uveal melanoma. The Colloborative Ocular Melanoma Group studied the prognostic value of gene expression profiling assay using 15 genes and reported their prospective study results in 2012. They classified the tumors as Type 1A, Type 1B and Type 2. The Type 1A tumors had a 2% chance of metastasis in 5 years, the Type 1B had 21% chance and the type 2 had a 72% chance of metastasis. This 15 gene-profiling assay is the most commonly used prognostic test in US currently. In addition to the gene profiling assay the other clinical parameter that has most significant prognostic importance is tumor size. Newer prognostic kits are also including Guanine nucleotide-binding protein G(q) subunit (GNAQ, or G-alpha-q) and GNA11 mutations in the testing algorithm. The estimation of risk of metastasis gives important information for screening but also now prophylactic treatments can be offered to high-risk patients. Currently prophylactic trials are open for Type 2 tumors with basal diameter larger than 12 mm, as these patients are at very high risk for metastatic disease. The chemotherapeutic agents that may show promise are Sunitinib (multi-targeted receptor tyrosine kinase inhibitor) and Crizotinib (antagonist to ALK (anaplastic lymphoma kinase)). The same gene profile assays can be used in iris melanoma also though the risk of metastasis is significantly lower compared to choroidal melanoma patients even if the cytogenetics is not favorable.

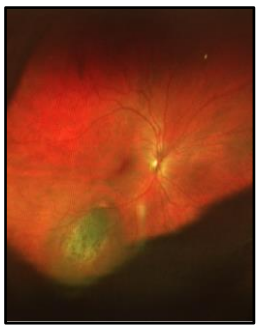
Conjunctival melanomas have a gene profile that is very different from uveal melanoma. The genetic makeup of conjunctival melanomas are similar to skin melanoma. BRAF and NRAS mutations are fairly common in conjunctival melanoma, whereas GNAQ/GNA11 mutations (which are seen in 80% of uveal melanoma) are not seen. BRAF mutated conjunctival melanomas have poorer prognosis and this information can be used therapeutically by using humanized antibody that targets the programmed cell death 1 (PD-1) receptor. Pembrolizumab is one such agent that was FDA approved in 2014 for use as a BRAF inhibitor in advanced melanoma patients who carry a BRAF mutation. Another agent that could potentially find use in conjunctival melanoma is Vemurafenib that only works in melanoma patients whose cancer has a V600E BRAF mutation.

At the University of Louisville Ocular Oncology Center, we obtain genetic profile on all patients with iris and choroidal melanoma using the multi-gene profiling assay. The tumor tissue is obtained at the time of either plaque radiation or enucleation. During plaque radiation a fine needle aspiration biopsy is performed either trans-sclerally or trans-vitreally (depending on tumor location). Tumor specimen is obtainable in approximately 92% of patients and tumor yield enough to provide prognostication is obtained in close to 85% patients. The complication rates are very small and persistent retinal or vitreous hemorrhage is the most common occurring in 1% of patients. In patients with conjunctival melanoma we routinely assess the BRAF mutation by obtaining samples during excisional biopsy. Patients at Lions Eye are treated in conjunction with melanoma oncologists at James Graham Brown Cancer Center. If patients are diagnosed with high-risk genetic profile then prophylactic chemotherapy is offered to them. The collaboration with systemic melanoma specialists has also benefitted patients with high grade conjunctival melanoma to consider prophylactic immunotherapy and in patients with documented systemic metastasis. In addition to clinical care, at University of Louisville we are also looking at early genetic markers for uveal melanoma so the malignant pathway can be blocked effectively.

Management of ocular melanoma has come a long way but metastatic disease still has a poor outcome and hence continued effort and research is needed to detect and treat patients that are at high risk for metastasis. Also it is critical to diagnose ocular melanoma early and to closely monitor suspicious lesions so early treatment can be instituted.

By: Aparna Ramasubramanian, MD

Figure Legend – Choroidal melanoma of right eye that was managed with plaque radiation and fine needle aspiration biopsy showed a Type 1A tumor indicating good prognosis.



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