Expression of Vascular Endothelial Growth Factor in Iris Melanoma

Uveal melanomas are the most common primary intraocular malignancy in adults. Iris melanomas constitute a small proportion of uveal melanomas with estimates ranging from 4% to 10%. Recent research in tumor microvasculature has emphasized vascular endothelial growth factor (VEGF) as a mediator of tumor angiogenesis. Considering its low metastatic potential (<5%), iris melanoma may be a good candidate for local therapy using anti-angiogenic agents directed against VEGF. To our knowledge, we present the first case of iris melanoma evaluated for VEGF.

Report of a Case. A 68-year-old woman was referred for the evaluation of an iris lesion in the left eye (Figure 1). Three weeks before our evaluation, she developed unilateral decreased vision. On examination, corrected visual acuity was 20/100 with no improvement with pinhole. A small hyphema was present in the anterior chamber. At the 5-o’clock meridian, there was a 2.5 × 1.6-mm, raised, vascular, non-pigmented mass on the iris, extending into the angle. The remainder of the eye examination results were unremarkable. Gonioscopy revealed several small, pale nodules in the inferior iridocorneal angle, separate from the main lesion. The patient underwent a diagnostic iridotrabeculectomy. Pathology specimens showed a spindle-type malignant melanoma of the iris as well as a melanoma nodule involving the adjacent iridocorneal angle tissue (Figure 2). Immunohistochemical staining for VEGF was positive using a rabbit antibody directed against human VEGF (Laboratory Vision Corporation/NeoMarkers, Fremont, Calif) (Figure 3).

Comment. Vascular endothelial growth factor is a 46-kDa glycoprotein that functions as an endothelial cell mitogen and a vascular permeability factor. It is thought to play a role in tumor angiogenesis. Some cutaneous melanomas have also been shown to express VEGF using immunohistochemical techniques. It has even been suggested that VEGF expression may be an unfavorable prognostic indicator in cutaneous disease. In normal retina and choroid, several studies have reported low levels or absence of VEGF immunoreactivity; however, VEGF is up-regulated in a variety of retinal ischemic diseases, such as prolif-
Intravitreal diabetic retinopathy, central retinal vein occlusion, and retinal detachment. Although data in the literature regarding the presence of VEGF in uveal melanoma are conflicting, our report shows the presence of VEGF in an iris melanoma.

Kvanta and colleagues demonstrated the presence of VEGF protein in retinoblastoma but not in posterior uveal melanomas. Similarly, in a study of VEGF expression in central retinal vein occlusion, Pe'er and coworkers used eyes with uveal melanoma as control specimens after finding that VEGF messenger RNA was undetectable or barely detectable in all 5 cases.

In contrast, Ijland and colleagues showed that human uveal melanoma cell lines expressed both VEGF and angiopoietin-2, a factor that appears to inhibit early maturation of newly formed vessels, suggesting that these tumors undergo a high degree of vascular remodeling. Two additional studies found 27% (10 of 37 eyes) and 22% (11 of 49 eyes) of uveal melanomas to be positive for VEGF protein on immunohistochemical staining. In a study by Sheidow and coworkers, 94% of 47 choroidal melanomas had VEGF-protein immunoreactivity. In a number of eyes with choroidal melanoma, evidence of breakdown of the blood-ocular barrier, including sites remote from the tumor such as the iris or ciliary body, suggests the presence of a soluble mediator of vascular permeability.

In the studies described earlier, investigators found high levels of VEGF protein centrally within the uveal melanoma and in the immediate perivascular distribution as well as in the adjacent retina and choroid. Likewise, VEGF receptor levels are elevated in the endothelial cells of the tumor vasculature and in uninvolved retina, choroid, and iris vasculature. The combination of up-regulation of VEGF receptors and elevated VEGF levels locally could explain the neovascularization responses seen in some eyes with intraocular melanomas.

Our patient had a vascularized iris mass with an associated hyphema. Histopathologic examination confirmed the diagnosis of iris melanoma and demonstrated that VEGF was indeed present. These findings are consistent with some recent studies that have found an association between uveal melanomas and VEGF expression. Future intraocular tumor therapy research targeting VEGF and its activity might also warrant an investigation of the applicability of this approach in the treatment of iris melanomas.

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