Iris Melanoma

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• The iris is the least common site of primary uveal melanoma. The prognosis of iris melanoma is better than that of melanoma of the ciliary body and choroid, but the reason for this difference is unclear. One possible explanation is that iris melanoma is smaller than its posterior segment counterparts at the time of diagnosis. Most iris melanomas are spindle cell types, according to a modified Callender classification system. There is evidence that the proliferation of melanocytes of the anterior iris surface (iris plaque) and diffuse stromal invasion may be risk factors for local recurrence and metastasis, respectively.

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Melanoma is the most common primary malignancy of the iris, but it accounts for only 3% to 10% of all uveal melanomas.[1,2] Because of its common histogenesis with ciliary body and choroidal melanoma, iris melanoma was initially assumed to have the same propensity to metastasize. The more favorable prognosis of iris melanoma, however, has forced closer examination of this assumption as well as a search for clues to explain differences in its biologic behavior.[3,4]

EPIDEMIOLOGY

The average age of patients diagnosed with iris melanoma is the mid to late 40s, which is approximately 10 years younger than the average age of patients with choroidal and ciliary body melanoma.[5–8] Most cancer registries do not distinguish anatomic location of uveal melanoma so there are few resources for determining the prevalence or incidence of iris melanoma. The Eye Pathology Institute of Denmark, Copenhagen, estimated an average of 6.5 cases of iris melanoma per 10 million population per year between 1961 and 1985.[9] There is no predilection for sex or laterality of eye, but about 80% of iris melanomas arise in the inferior half of the iris.[7] Iris melanomas are considerably smaller than choroidal melanomas at the time of diagnosis, averaging less than one fifth their volume.[10] Although iris melanomas tend to occur in persons with fair complexions,[3] only 1 study involving 23 patients with iris melanoma has been conducted showing an association with light iris color.[11] This association is similar to the relationship that choroidal melanoma has to light iris color.[12]

CLINICAL FEATURES

Iris melanomas display 2 patterns of growth: circumscribed and diffuse. Most circumscribed iris melanomas have a yellow, tan, or brown color with flat or rounded anterior contour (Figure 1).[1,3] Most are discovered on routine examination or are noticed by patients or friends of patients as an asymptomatic pigmented spot. Diffuse melanomas, on the other hand, usually present as a unilateral dark iris (heterochromia) without focal thickening (Figure 2).[13] A substantial proportion of diffuse melanomas are complicated by glaucoma, which is often because of tumor involvement of the trabecular meshwork.[13] Iris melanomas that have little clinically detectable pigmentation resemble tapioca.

The most common problem encountered in the clinical evaluation of a circumscribed pigmented lesion of the iris is distinguishing melanoma from nevus.[1] There is no absolute cutoff in size between a small iris melanoma and large nevus, but findings such as prominent tumor vascularity, elevated intraocular pressure, and tumor seeding within the anterior chamber increase the likelihood of malignancy.[1] Although documented growth using serial slit lamp photography provides substantive evidence of melanoma, some iris nevi have been shown to enlarge when monitored for growth in this manner.[1] Other lesions that can clinically mimic a circumscribed melanoma include primary iris cysts (posterior epithelial or stromal), adenoma of the iris epithelium, iris metastasis, occult iris foreign body, and iris leiomyoma.[1,14] Recent generation ocular ultrasound has significantly enhanced noninvasive diagnostic capabilities. Anterior segment ultrasound permits monitoring of iris thickness, detection of tumor involvement into the ciliary body, and identification of iris cysts, to name just some of its capabilities.[14]

The differential diagnosis of a unilateral dark iris (ie, heterochromia) includes diffuse iris nevus, melanosis oculi, ocular hemosiderosis, ocular siderosis from a retained iron foreign body, essential iris atrophy, and increased melanogenesis from topical prostaglandin agonists.[1,3]

Although the diagnosis of iris melanoma can be arrived at without tissue confirmation prior to therapeutic intervention, if any uncertainty exists, intraocular biopsy either incisional or fine-needle aspiration technique (modified ''vacuum'' aspiration) is recommended.[15,16] Incision biopsy is more invasive than needle biopsy but provides a better specimen. Because seeding of iris melanoma cells along the biopsy tract is a potential complication of the procedure, a clear corneal approach is recommended.[15,16]

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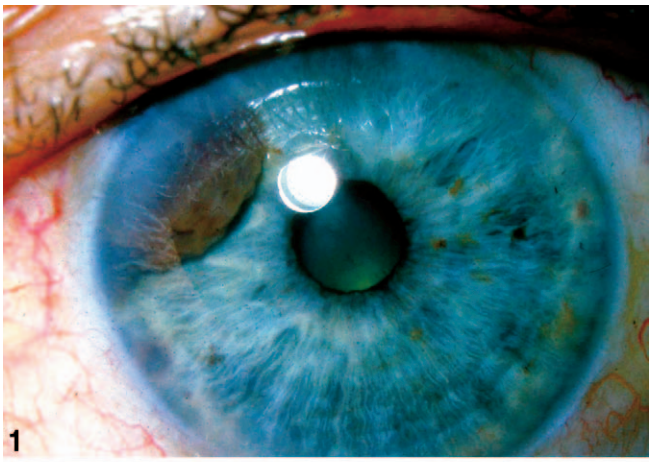

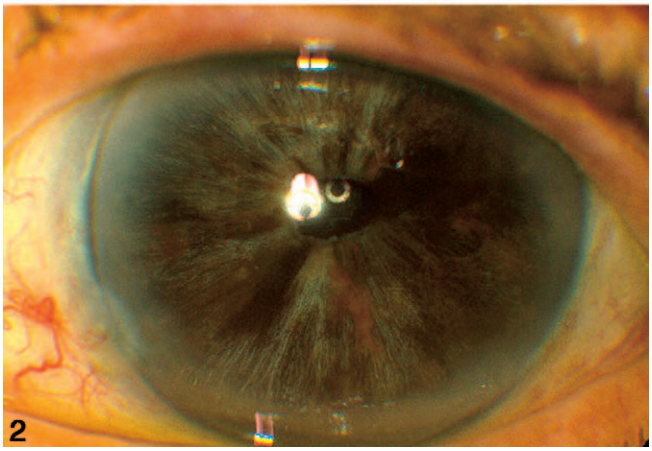

Figure 1. *Circumscribed iris melanoma at approximately 10 o'clock position. The brown tumor arises at the root of the iris and protrudes into the anterior chamber.*

Figure 2. *Diffuse iris melanoma just prior to diagnostic iridectomy. The iris developed its brown and gray color during 1 year. The opposite eye was blue.*

RISK FACTORS

Other than fair skin color and blue to gray iris color, there are few known risk factors for iris melanoma.[12] Epidemiologic studies have yielded inconsistent results concerning the association of uveal melanoma to sunlight exposure.[17] There are no analytical studies that specifically address the relationship of iris melanoma to ultraviolet light exposure.

The increase in lifetime risk of uveal melanoma for persons with oculodermal melanocytosis (nevus of Ota and melanosis oculi) includes iris melanoma.[18] Four cases of iris melanoma have been reported in patients with neurofibromatosis. Despite the neural crest origin of both conditions, the rare occurrence of iris melanoma and neurofibromatosis may be no more than coincidental.[19]

HISTOPATHOLOGY

The modified Callender classification used for uveal melanoma is recommended for iris melanomas.[20,21] The system recognizes 2 cellular types of melanoma cells (spindle and epithelioid) and 3 categories of melanoma (spindle cell, epithelioid cell, and mixed cell type).[20,21]

Typical spindle uveal melanoma cells have a plump but elongated nucleus, mildly coarse chromatin, and an identifiable eosinophilic nucleolus (Figure 3, A and B). A longitudinal fold in the nuclear envelope of some cells gives the impression of a chromatin streak. By comparison, epithelioid cells are larger and more pleomorphic. The abundant eosinophilic cytoplasm and distinct cells borders

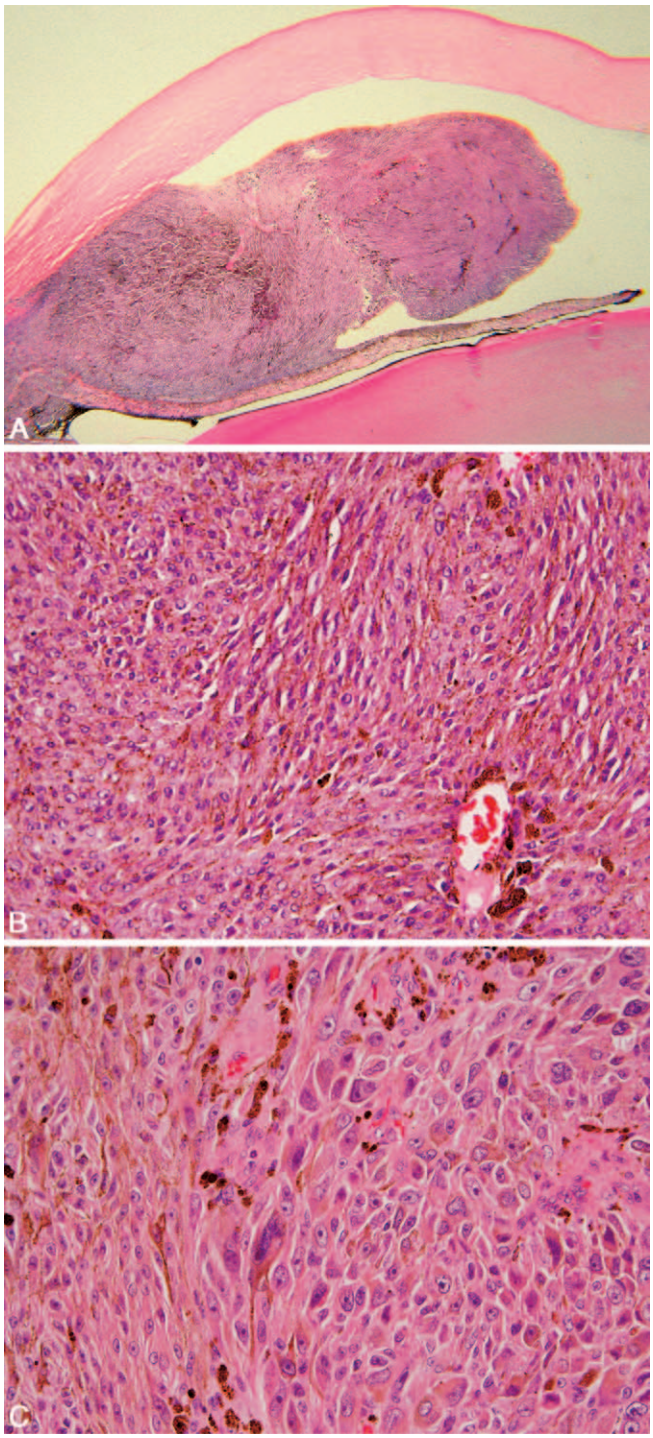

Figure 3. *A, Circumscribed iris melanoma fills the anterior chamber. The tumor is cellular and bulky (hematoxylin-eosin, original magnification ×2). B, A majority of the tumor was composed of relatively uniform spindle melanoma cells, most of which contain visible melanin (hematoxylin-eosin, original magnification ×40). C, A minority of the tumor contained epithelioid cells, characterized by their larger size, greater pleomorphism, eosinophilic cytoplasm, and larger nuclei with prominent nucleoli (hematoxylin-eosin, original magnification ×40).*

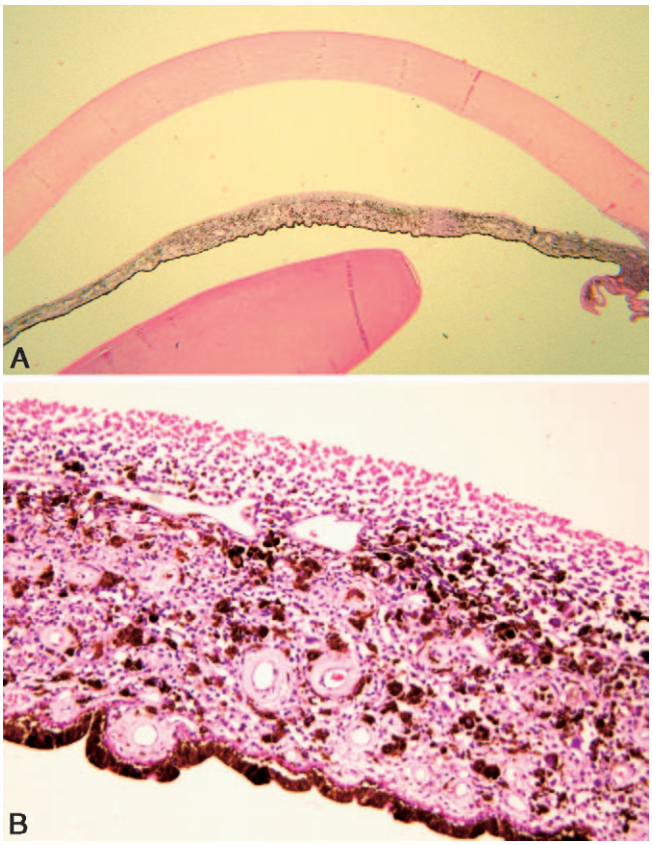

Figure 4. *A, Enucleated eye sectioned eccentric to the pupil showing diffuse iris melanoma. The iris is normal in thickness (hematoxylin-eosin, original magnification ×2). B, The iris stroma is replaced by small- to medium-size undifferentiated melanoma cells. The anterior iris surface is covered by necrotic cells. The consensus opinion of ophthalmic pathologists who reviewed this case was small epithelioid cell type (hematoxylin-eosin, original magnification ×25).*

gives epithelioid cells their superficial resemblance to true epithelium (Figure 3, C). The larger nucleus of the epithelioid cell has coarse marginated chromatin and a centrally placed nucleolus. Mitotic activity within uveal melanomas is usually low but is typically greater among populations of epithelioid cells than spindle cells.

Although the distinction between circumscribed and diffuse iris melanoma is made clinically, the difference between the 2 patterns of growth can also be seen by light microscopy (Figure 4, A and B).

Like all artificially created systems of classification, the modified Callender system must contend with the difficulty of placing cells that exist along a morphologic continuum into discrete categories. There are also no precise guidelines for minimal proportion of spindle cells (or epithelioid cells) needed to diagnose mixed cell type melanoma. In a study conducted by the Armed Forces Institute of Pathology for the World Health Organization, at least 2 of 5 ophthalmic pathologists disagreed on the classification of cell type 60% of the time.[20]

More than half of all iris melanomas reported in the literature are diagnosed as spindle cell melanoma.[4] For purposes of comparison, most choroidal melanomas (approximately 85%) are mixed cell type and only 9% are classified as spindle cell.[22]

Three benign primary melanocytic tumors of the iris have been recognized: spindle cell nevus, epithelioid cell nevus, and melanocytoma.[1,20,23] Each is characterized by a high cytoplasm-nuclear ratio, delicate nuclear chromatin, inconspicuous or absent nucleoli, and no mitotic activity. The distinction between epithelioid cell nevus and melanocytoma is based on the heavy melanin content of melanocytoma cells.[20] Bleached sections are usually required to study cellular detail of melanocytoma. The propensity of melanocytoma to undergo spontaneous necrosis can confound histologic diagnosis.

Investigation into quantitative methods of measuring cellular pleomorphism of iris melanoma has been limited. A study of melanocytic tumors of the iris that compared histopathologic classification with DNA content and selected morphometric parameters found a correlation between nevus and melanoma to nucleolar size (larger size for melanoma) but no correlation for DNA ploidy.[24]

Worse survival of choroid and ciliary body melanoma has been associated with certain microvascular patterns detectable with periodic acid–Schiff stain. One study compared the microvascular patterns of iris melanomas to those of ciliary body and choroidal and found that iris tumors lacked high-risk patterns (parallel vessels with cross-linking and networks of back-to-back loops).[25] Although this is consistent with the better prognosis of iris melanoma, the importance of microvascular patterns as an independent predictor of survival remains to be determined.[26]

IMMUNOHISTOCHEMISTRY

Markers of melanocytic differentiation have a limited role in routine histologic evaluation of pigmented tumors of the iris. HMB-45, S100 protein, and neuron-specific enolase are not useful in distinguishing uveal melanoma from nevus.[27] HMB-45 has greater sensitivity and specificity for uveal melanocytic proliferations than either S100 protein or neuron-specific enolase and would accordingly find practical application in the evaluation of nonpigmented iris tumors.[20] Other melanocytic markers, including Melan-A, tyrosinase, and microphthalmia transcription factor, are expressed in uveal melanomas but currently offer no known advantage in routine diagnostic evaluation.[28] There is no known difference in the pattern of immunophenotype expression of iris and posterior segment melanomas, although there has been little study in this area.

A variety of immunohistochemical markers for growth factors, proliferation molecules, adhesion molecules, transcription factors, signaling molecules, proteases, and other proteins have been used to study uveal melanoma. Most have been used to better elucidate the pathogenesis of posterior segment tumors. The role of p53 and Ki-67 in modulating cell growth was investigated in 18 iris melanomas.[29] When compared with posterior segment melanomas, the proliferative activity of the iris tumors was less.

TREATMENT

Once the diagnosis of iris melanoma is established based on clinical examination alone, or through biopsy, the treatment options are limited. Some small, circumscribed iris melanomas can be observed, particularly in persons with comorbidities that limit life expectancy. Most discrete lesions with documented growth are excised surgically, preserving visual function.[1,30] Iris tumors that involve the angle of the anterior chamber require partial resection of the ciliary body, which increases ocular morbidity. Radiotherapy has a limited role in the management of a resect-

able iris melanoma because of the greater likelihood of vision-related complications. Large tumors or diffuse melanomas involving more than half (6 clock hours) of the iris usually require enucleation, especially if glaucoma or invasion of the trabecular meshwork is present. In monocular patients, or in persons unwilling to undergo surgery, specially designed radioplaques can be attempted.[13]

Assessing the surgical margins of an en bloc resection of uveal melanoma is difficult because it requires proper orientation of a small specimen and because uveal tissue is easily crushed by handling. Although no single technique is considered a standard, accurate orientation requires communication with the surgeon.[31]

PROGNOSIS

The importance of cell type in determining prognosis has been well documented for uveal melanoma of the posterior segment. In terms of survival, choroidal and ciliary body melanomas composed exclusively of spindle melanoma cells have the most favorable prognosis, epithelioid tumors the worse, and mixed cell type melanomas intermediate.[20,21] Although the favorable prognosis of spindle cell melanoma of the iris is well established,[3,20] it is unclear if a survival difference exists among patients with mixed cell type and epithelioid iris melanoma.[3,4]

Geisse and Robertson[4] surveyed 1043 iris melanomas reported in the literature and calculated an overall rate of metastasis of 3%. The rates of metastasis according to cell type were 2.6%, 10.5%, and 6.9% for spindle, mixed, and epithelioid cell types, respectively. These rates need to be interpreted cautiously, however, because in 40% of cases culled from the literature no histopathologic classification of cell type was included and many patients had limited or no clinical follow-up.[4]

The proportion of iris melanomas that develop documented metastases reported in clinical series ranges from 0% to 10%.[5–9,20,23,30,32] Most of these studies had problems obtaining long-term clinical follow-up. Lack of follow-up introduces a bias toward survival, particular for tumors such as uveal melanoma that may be prone to late recurrence.[3] The longest latency between treatment of an iris melanoma and first metastasis is 17 years.[33]

In a review of 189 archived melanomas of the iris and iris-ciliary body from Cornell University College of Medicine, 87% were reclassified as benign (benign melanocytosis or iris nevus).[23] Thirty-six of the 42 incompletely excised tumors in the series did not recur during a median follow-up of 8 years. Three of the 6 patients with local recurrences had cytologically benign nevi with surface melanocytic growth observed on the primary biopsy (termed *surface plaque* by the authors[23]). As a result of this observation, surface plaque was proposed as a risk factor for local recurrence.[23] Despite the relatively long period of postoperative surveillance, 26% of patients had no follow-up. Because of the absence of metastases and tumor-related death, it was concluded that most melanocytic tumors of the iris are biologically benign and do not require aggressive surgical intervention.[23]

In another series of 51 iris melanomas from the University of Sydney, Sydney, Australia, there were no documented metastases during a median follow-up of 8.7 years.[30] Most patients were treated conservatively and 8% were lost to follow-up.

The 2 studies just cited, which reported the lowest rates of metastasis, contrast to a 25-year analysis of iris melanomas from the Eye Institute of Denmark.[9] In this survey of 80 patients, in which no patient was lost to follow-up, there was a 10% tumor-related mortality.[9] In none of the studies so far discussed, however, were the differences in length of patient follow-up dealt with using the life table method of survival analysis (eg, Kaplan-Meier), which takes into account how variable lengths of follow-up influence the probability of survival (or metastasis).

A study from Wills Eye Hospital reviewed the outcome of 169 consecutive patients with tissue-confirmed diagnoses of iris melanoma.[32] Using Kaplan-Meier analysis, the 5-, 10-, and 20-year risk of metastasis was 3%, 5%, and 10%, respectively.[32] The proportion of patients with metastatic disease doubled between 10 and 20 years, suggesting that the length of follow-up in many earlier studies may have been too short to capture a substantial number of tumor-related deaths.

When mortality is examined by pattern of growth, diffuse iris melanomas appear to have a higher rate of metastasis compared with circumscribed tumors. In a study of 25 patients with diffuse melanoma, defined as involving more than half (6 or more clock hours) of the iris with no distinct tumor nodules, the metastatic rate was 13% (mean follow-up, 78 months).[13]

There is conflicting information on the cellular composition of diffuse melanomas. In the study just cited, 80% of tumors were diagnosed as epithelioid melanoma.[13] In a comprehensive review of diffuse iris melanoma, Brown and colleagues[34] could document only 4 epithelioid melanomas among 38 cases published in the literature. The remaining cases of diffuse melanoma with recorded histology were divided equally between spindle and mixed cell types.

SUMMARY

The modified Callender system, which consists of 3 cytologic categories of melanoma (spindle cell, epithelioid cell, and mixed cell types), is used to classify iris melanomas just as it is for other uveal melanomas.[20,21] In addition, 3 types of melanocytic nevi have been described in the iris: spindle cell, epithelioid cell, and melanocytoma.[1,20,23] Although overall prognosis for iris melanoma is good, variability in the rates of metastasis reported in the literature may reflect differences in completeness and length of clinical follow-up.[3,4] There is evidence that survival is worse for iris melanomas that diffusely replace iris stroma compared with tumors having circumscribed patterns of growth.[13,32,34]

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