Intraocular Astrocytoma and Its Differential Diagnosis

Allen Pusateri, MD; Curtis E. Margo, MD, MPH

• Astrocytomas arising within the eye display 2 distinct histologies: one comprises interlacing bundles of spindle-shaped cells mixed with a minority of polygonal cells, and the other consists of large cells with abundant glassy cytoplasm (gemistocytic astrocytes) indistinguishable from cells found in subependymal giant cell astrocytoma. Both histologic patterns express glial fibrillary acid protein diffusely, are biologically benign, and are frequently associated with dysgenic syndromes, particularly tuberous sclerosis complex. Tumors with gemistocytes, however, demonstrate a greater propensity for invasive growth. The clinical history may provide information to guide the pathologist in distinguishing intraocular astrocytoma from reactive astrocytosis, conditions that are histologically similar. It remains to be determined if other types of primary intraocular glioma exist or whether some degree of ependymal or oligodendroglial differentiation can accompany reactive astrocytosis.

(*Arch Pathol Lab Med*. 2014;138:1250–1254; doi: 10.5858/arpa.2013-0448-RS)

The term *intraocular astrocytoma* describes a low-grade neoplasm that arises in the retina and/or optic nerve anterior to the lamina cribrosa scleralis (optic nerve head). Astrocytomas in this location are distinguished conceptually from astrocytic hamartomas and reactive astrocytosis (so-called massive gliosis) by progressive, autonomous growth. In clinical practice, however, the distinctions among astrocytic neoplasia, hamartoma, and reactive astrocytosis are sometimes blurred. Intraocular astrocytomas are biologically benign, but they can result in considerable ocular morbidity and loss of vision. Due to ample histologic similarities among the nosological categories described above, clinical correlation and, at times, molecular genetic analysis, may contribute to diagnostic certitude. In this review, *intraocular astrocytoma* will supersede the popular but less precise term *intraocular glioma* because intraocular oligodendroglioma and ependymoma have been reported.

Accepted for publication October 2, 2013.

From the Department of Pathology and Molecular Biology, Morsani College of Medicine, University of South Florida, Tampa (Dr Margo). Dr Pusateri is a resident in training at the Department of Ophthalmology, Morsani College of Medicine, University of South Florida, Tampa.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Curtis E. Margo, MD, MPH, Department of Pathology and Molecular Biology, Morsani College of Medicine, University of South Florida, MDC Box 79, 12901 Bruce B. Downs Blvd, Tampa, FL 33612 (e-mail: cmargo@health.usf.edu).

EPIDEMIOLOGY

Intraocular astrocytoma is uncommon, can exist without causing symptoms, and is a presumptive diagnosis when based on clinical grounds alone. These factors contribute to the lack of population-based estimates of its prevalence. In the largest review of gliomas of the anterior visual pathway to date, 1.6% of 1278 tumors were located in the optic nerve head.[1] This proportion, however, does not include astrocytomas that arose in retina, nor does it address the denominator population from which the cases were drawn. In a review of 42 intraocular astrocytomas confirmed histologically, 57% were associated with tuberous sclerosis, 14% were related to neurofibromatosis, and 29% were sporadic.[2] The literature reflects roughly one-half to two-thirds of intraocular astrocytomas linked to a dysgenic syndrome or with retinitis pigmentosa.[2–5] Tuberous sclerosis complex (TSC), whose estimated prevalence is about 1 per 10 000, is the single most common inherited disorder associated with intraocular astrocytoma.[6] About half of the patients with TSC have astrocytic tumors of the retina or optic nerve head, most of which are clinically stationary lesions classified as hamartoma.[3,7]

CLINICAL PERSPECTIVE

Most eyes with histologically confirmed astrocytoma are removed surgically because of blindness and pain or because they simulated retinoblastoma in children or amelanotic melanoma or metastatic carcinoma in adults. Age at presentation has ranged from 1 month to 45 years, and tumors have ranged in size from several millimeters to masses that fill the globe.[2,8–12] Roughly one-half of tumors contain deposits of calcium; some astrocytomas shed cells into the vitreous, a behavior that raises suspicion of retinoblastoma, in particular.[13]

In contrast to astrocytoma, typical astrocytic hamartomas of retina or optic nerve head are discrete white to yellow masses with gelatinous or semitranslucent appearance on ophthalmoscopy.[3] They range in size from less than 1 mm to greater than 5 mm and remain stable or display minimal enlargement with time.[3,7] When stippled with spherical calcium deposits (calcospherites), they have been likened to a mulberry or tapioca. Clinically, a typical astrocytic hamartoma in a person with tuberous sclerosis can usually be monitored for growth with photography, fluorescein angiography, or optic coherence tomography.

Reactive retinal astrocytosis generally does not enter the clinical differential diagnosis of intraocular astrocytoma, despite their histopathological similarities. Various reasons for this divergence in clinical and pathological interpretation

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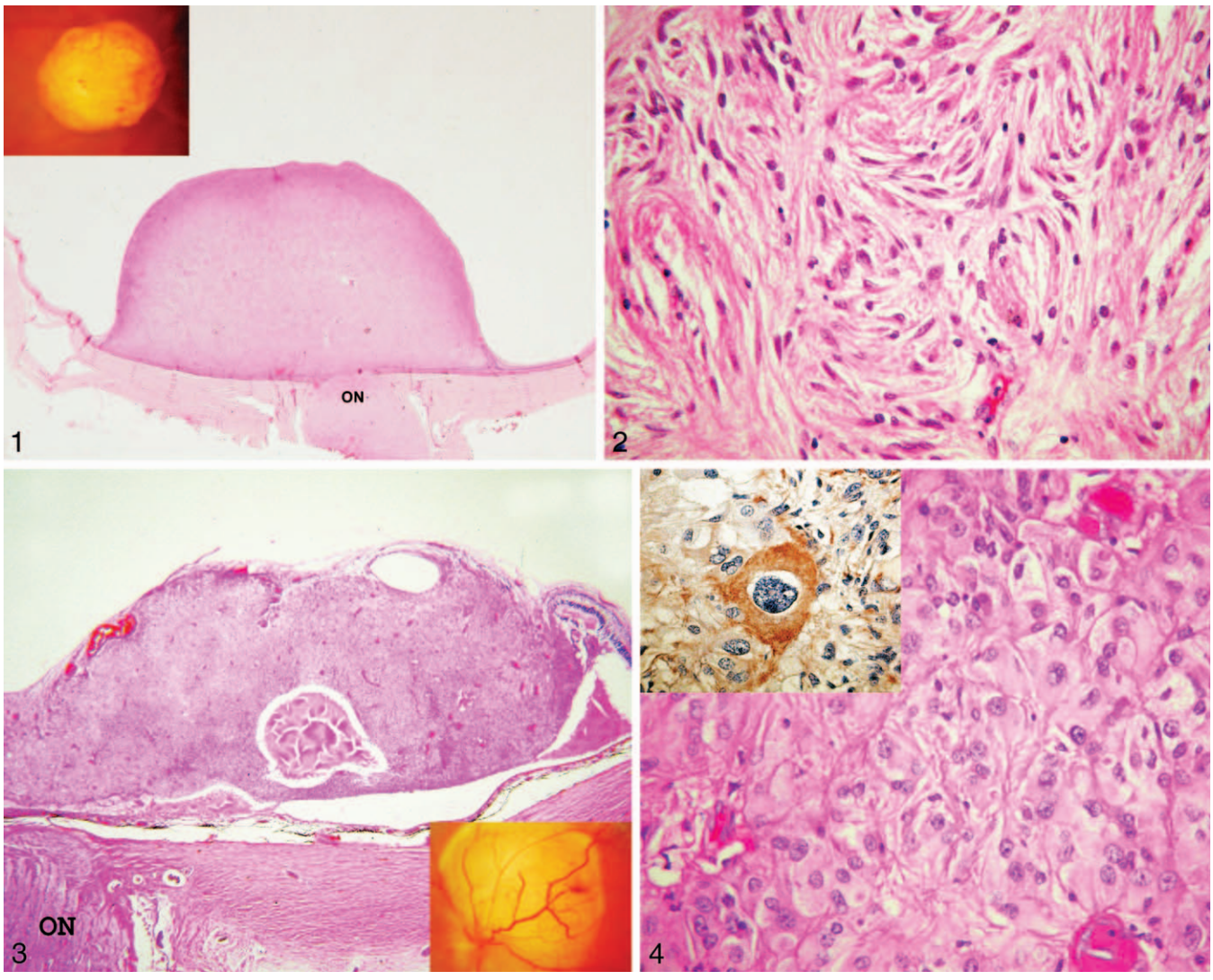

Figure 1. *Dome-shaped astrocytoma rests on optic nerve (ON). The tumor does not invade choroid or optic nerve (hematoxylin-eosin, original magnification ×5). The inset shows this tumor before enucleation and after 2 years of documented growth. The 8-year-old boy had no dysgenic syndrome.*

Figure 2. *The tumor in Figure 1 consists of spindle cells arranged in interwoven bundles (hematoxylin-eosin, original magnification ×200).*

Figure 3. *An astrocytoma has effaced the retina and overlaps the optic nerve (ON). Pink subretinal exudate surrounds the tumor, and a pool of exudate is noted within the tumor (hematoxylin-eosin, original magnification ×12). The inset shows this nonpigmented tumor before enucleation residing temporal and superior to the optic nerve. The patient had tuberous sclerosis.*

Figure 4. *The tumor in Figure 3 consists of large cells with abundant pink cytoplasm and round nuclei (hematoxylin-eosin, original magnification ×200). The inset shows cells with great variability in size that stain positive for neuron-specific enolase (immunoperoxidase, original magnification ×200).*

exist, but 2 explanations seem most plausible. First, the diagnosis of reactive astrocytosis may not be entertained because it develops in an eye already affected by a known primary condition such as retinopathy of prematurity or proliferative diabetic retinopathy; second, in eyes without preexisting disease, prominent vascularity or vascular exudation often dominates the clinical picture, which directs diagnostic consideration toward retinal vascular disorders.[14–17] The seminal article on reactive astrocytosis coined the phrase massive gliosis of the retina, although some of the lesions were relatively small and discrete.[18] Larger lesions among the 38 eyes in this series were associated with insults that occurred during childhood and had long intervals to enucleation.

HISTOPATHOLOGY

The cytological features of the majority of astrocytes that make up exophytic tumors of the retina or optic nerve head consist of an elongated spindle cell with ill-defined cytoplasm and oval to round nucleus (Figures 1 and 2). These fibrous astrocytes are often arranged in interwoven fascicles and admixed with foci of polygonal cells with eosinophilic cytoplasm. Mitotic activity is not observed. Calcium deposits are common, but necrosis is not. Rosenthal fibers and granular bodies, although conceivable in the context of low-grade astrocytoma, have not been documented to date. No differences exist in the histopathology of sporadic and syndrome-associated tumors.[2]

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The other subset of astrocytoma is characterized by a more heterogeneous population of cells, many of which have abundant glassy, eosinophilic cytoplasm (gemistocytic astrocyte). Their nuclei are round to oval and can have prominent nucleoli (Figures 3 and 4). Calcospherites and occasionally metaplastic bone are described.[19] Necrosis is common among these tumors, but mitotic figures are rare or absent.[8,19,20] Local invasion of the choroid and scleral emissary canals has been reported, and several tumors have extended immediately behind the lamina scleralis of the optic nerve.[8,19,20] This subset has been designated giant cell astrocytoma of retina because of its resemblance to subependymal giant cell astrocytoma of TSC. Ocular giant cell astrocytoma, however, has been described in patients with and without the genetic mutation.[8,9,19,20] Although relatively few cases have been reported, the most locally aggressive of these tumors contain calcium, display more than 50% necrosis, and cause neovascularization of the iris.[8,10,19,20]

IMMUNOHISTOCHEMISTRY

Glial fibrillary acid protein (GFAP), the cytoplasmic intermediate filament of normal and neoplastic astrocytes, and S100 protein are diffusely expressed in intraocular astrocytomas.[2,8–10] Most tumors are neuron-specific enolase negative, but gemistocytic cells coexpress neuron-specific enolase in addition to variable staining with GFAP and S100 (Figure 4, inset).[8–10,20]

DIFFERENTIAL DIAGNOSIS

Relatively few astrocytic hamartomas of the retina and optic nerve head have been examined histologically. They are usually encountered as coincidental findings at autopsy, for example. Astrocytic hamartomas typically occupy the inner retina and consist of delicate spindle cells with indistinct cell borders and oval nuclei.[21] Occasionally, fibrous astrocytes are obscured by myriad calcospherites.

The tumorlike lesions of reactive astrocytosis range in size from a few millimeters or less to masses that obliterate the vitreous cavity (Figure 5). Large lesions, often referred to as massive gliosis, consist of spindle and polygonal fibrous astrocytes, virtually identical to those found in astrocytomas (Figures 6 and 7).[14] Cells are immunoreactive for GFAP and S100 but not enolase.[22,23] Thick-walled vessels are dispersed throughout the interweaving fascicles. Metaplastic bone, occasionally with marrow elements, is usually present peripherally, as are retinal pigment epithelial hyperplasia and retinal pigment epithelial fibrous metaplasia. The diagnosis of secondary astrocytosis is further supported by signs of past trauma or surgery, or with other evidence of preexisting eye disease.

Smaller reactive astrocytic lesions, so-called vasoproliferative tumors, are composed of interlacing bundles of GFAP-positive spindle cells and contain widely separated hyalinized vessels along with intraretinal and subretinal exudate. Metaplastic bone, hyperplastic retinal pigment epithelium, Rosenthal fibers, and granular bodies are reported.[17] These lesions are not invasive, and the Ki-67 index is less than 1%.[17] Unlike most low-grade astrocytomas of the brain, they do not overexpress p53, nor do they display the *K1AA-BRAF* fusion mutation seen in pilocytic astrocytoma.[17]

Two studies[24,25] of retinal ependymoma describe tumors that are similar by light microscopy to massive astrocytosis of the retina, with the exception of scattered cytoplasmic immunoreactivity for epithelial membrane antigen and a few extracellular lumina that were highlighted by the stain. Both of these retinal ependymomas occurred in eyes that had been phthisical for decades.

Retinal hemangioblastoma is unlikely to create confusion histologically with the astrocytic lesions described above. This is because of its characteristic vacuolated interstitial cells and endowment of fine capillaries (Figure 8).[26]

To date, no oligodendroglioma of the retina has been satisfactorily documented. An initial case report of a retinal oligodendroglioma[27] probably represented a retinocytoma, the benign variant of retinoblastoma.[28] Retinocytomas are composed of cytologically bland neuroepithelial cells with abundant clear to eosinophilic cytoplasm. Linear arranged groups of cells with pink cytoplasmic projections (so-called fleurettes) are typically sprinkled throughout these tumors. When studied ultrastructurally, the cytoplasmic projections correspond to the outer portion of a photoreceptor.[28]

Other primary intraocular tumors have little histologic similarity to astrocytic proliferations. Retinoblastoma and medulloepithelioma are highly cellular tumors, often containing neuroepithelial rosettes. Rare spindle cell tumors like leiomyoma, neurilemmoma, and neurofibroma do not arise in neurosensory retina, and, if needed, these lesions could be distinguished from astrocytoma by appropriate immunohistochemical stains.

PATHOGENESIS

A substantial proportion of intraocular astrocytic hamartomas and astrocytomas described in the literature has been associated with TSC, a single-phenotype systemic disorder related to mutations in 2 distinct genes (*TSC1* and *TSC2*).[1,3,7] Tuberous sclerosis complex is caused by loss of function in 1 of these 2 genes, which normally function to suppress the P13K signal transduction pathway.[6] The proteins encoded by the genes are hamartin and tuberin, which bind one another to form a molecular complex that influences cellular growth and survival.[6]

Neurofibromatosis type 1 is less often linked to intraocular astrocytomas than TSC, yet it is the most common genetic syndrome associated with anterior visual pathway astrocytomas.[29] Molecular alterations in astrocytomas tend to vary by site, so the findings in optic nerve gliomas, for instance, may not necessarily apply to tumors located in other locations like the retina. Nonetheless, *NF1*-associated pilocytic astrocytomas are due to homozygous inactivation of the *NF1* gene. Sporadic tumors with the same morphology in the cerebellum and optic nerve can occur independent of the *NF1* mutation[30]; when they do, these astrocytomas are related to *BRAF* duplication and MARK pathway activation. It is unknown whether similar mutations are operational in sporadic retinal astrocytoma.

CONCLUSION

Intraocular astrocytomas are rare neoplasms distinguished clinically from hamartomas by their larger size, progressive growth, and invasion of ocular tissues. Histologically, they consist of bland spindle-shaped and polygonal fibrous astrocytes, or large cells with glassy, eosinophilic cytoplasm, similar to gemistocytes of subependymal giant cell astrocytoma. Although this latter subset of tumor can be locally aggressive, it has not resulted in orbital recurrence or metastasis to our knowledge. Clinical history and genetic studies can provide valuable information if the histologic

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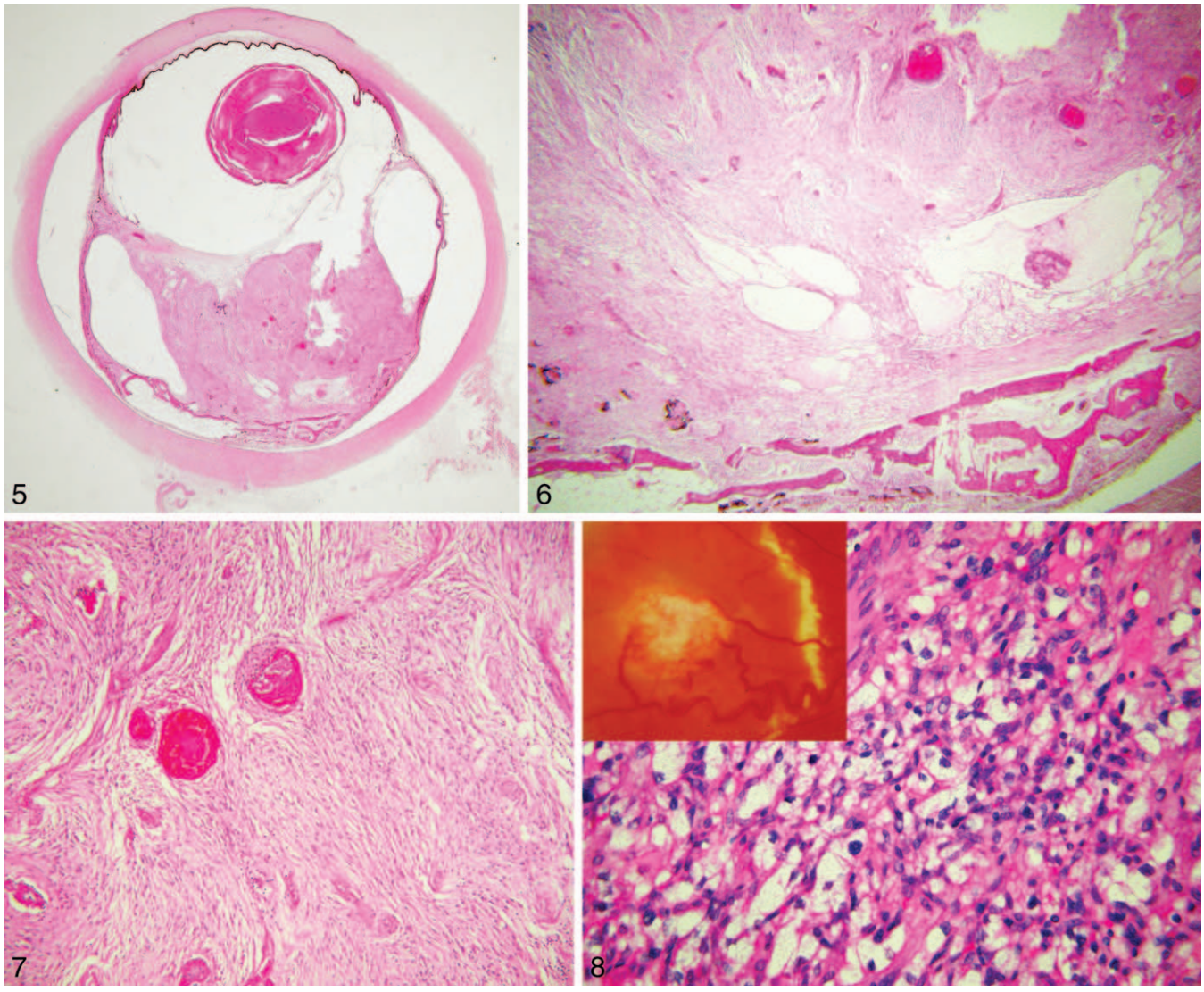

Figure 5. *Eye of a 37-year-old man who was blind since childhood from retinopathy of prematurity. About one-third of the eye is filled with pink tissue (hematoxylin-eosin, original magnification ×2.5).*

Figure 6. *Intermediate magnification of the eye in Figure 5 shows a spindle cell proliferation, cystic spaces, and dilated vascular channels. Osseous metaplasia and retinal pigment epithelial hyperplasia are noted posteriorly just inside the scleral tunic (hematoxylin-eosin, original magnification ×20).*

Figure 7. *The cells occupying the vitreous space are bland spindle-shaped astrocytes. Numerous dilated vascular channels are present (hematoxylin-eosin, original magnification ×200).*

Figure 8. *Retinal hemangioblastoma with vacuolated interstitial cells admixed with almost imperceptible small capillaries (hematoxylin-eosin, original magnification ×200). The inset shows the clinical appearance of a retinal hemangioblastoma from another patient. Prominent feeder vessels and subretinal exudate are present. Reprinted with permission from Martin Orlick, MD.*

distinction between astrocytoma and reactive astrocytosis is indeterminate. More sensitive and specific markers to distinguish low-grade astrocytoma from reactive gliosis will be welcome diagnostic adjuncts as intraocular biopsy evolves as a clinical resource. It remains to be determined whether retinal ependymoma is a distinct primary glioma or a pattern of reactive gliosis involving cells that retain the capacity of ependymal differentiation.

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