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Reactive Retinal Astrocytic Tumors (So-called Vasoproliferative Tumors): Histopathologic, Immunohistochemical, and Genetic Studies of Four Cases

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Abstract

Purpose—To evaluate the cellular nature of and diagnostic terminology used in connection with acquired retinal “vasoproliferative tumors.”

Design—Retrospective clinicopathologic study.

Methods—Clinical records and microscopic slides of 4 enucleated globes were reviewed. Special stains and immunohistochemical probes for CD31, CD34, p53, glial fibrillary acidic protein (GFAP), CD163, and Ki67 (cell replication) were employed; ultrastructural and fluorescence in situ hybridization (FISH) analyses were performed.

Results—Tumors were located inferotemporally in middle-aged patients. They were uniformly composed of compacted elongated, GFAP-positive spindle cells (due to intermediate filaments identified ultrastructurally) with a Ki67 index of less than 1%. Rosenthal fibers and eosinophilic granular bodies were observed. Hyalinized periodic acid–Schiff-positive vessels were widely separated. CD31 and CD34 revealed a sparse microvasculature. Tumor-associated exudate spread predominantly subretinally. The retinal pigment epithelium had undergone extensive placoid fibrous metaplasia with focal ossification. P53 upregulation, *BRAF-KIAA* gene rearrangement, and *IDH1 R132H* mutation typically associated with low-grade astrocytic neoplasms were absent.

Conclusions—Retinal “vasoproliferative” tumors have been mischaracterized, because they actually display a paucity of microvessels. Proliferating fibrous astrocytes with a very low

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proliferation index predominate, without immunohistochemical or genetic evidence favoring a neoplasm. Subretinal exudate appeared capable of provoking widespread fibrous metaplasia of the pigment epithelium that was mainly responsible for secondary retinal damage. The term “reactive retinal astrocytic tumor” is proposed as more appropriate for this entity. In carefully selected progressive lesions, consideration should be given to earlier surgical intervention before extensive subretinal exudate accumulates and pigment epithelial proliferation with fibrous metaplasia ensues.

Acquired retinal tumors containing both vascular and glial components were first described by Shields and associates in 1983 in a series of 12 cases.[1] Their initial term for this condition was “acquired retinal hemangioma,” based on the fluorescein angiographic features. Subsequently, the same ocular oncology service reported a series of 103 patients with 129 tumors in 1995; at that time, the authors rechristened the lesions “vasoproliferative tumors of the retina” (VPTR).[2] Many other synonyms have thereafter been employed—“acquired retinal angioma,”[3] “angioma-like mass” in retinopathy of prematurity,[4] “retinal angiomatous mass” after retinal detachment surgery,[5] “retinal angiomas in the aged,”[6] “angioma-like lesion” in sickle cell disease,[7] “goangiosis,”[8] “presumed acquired retinal hemangioma,”[1] “hemangioma-like masses of the retina,”[9] “peripheral retinal telangiectasia” simulating melanoma,[10] “peripheral uveal neovascularization,”[11] and “neovascular fundus abnormality” in patients with uveitis[12] —all of which share an emphasis on vasogenesis as the essential pathologic substrate. There are, however, few studies on the histopathologic features of these lesions upon which to judge their true nature.[8,13-15] We have been able to evaluate 4 globes harboring these tumors with in-depth histopathologic, immunohistochemical, ultrastructural, and genetic studies. Specifically, our first objective is to determine whether vasoproliferation or progressive astrocytic proliferation drives the condition. Secondly, if the astrocytes are basically responsible for the formation of the tumors and their progressive enlargement, are they reactive or neoplastic?

Methods

This Study was Performed Under the Auspices of the Massachusetts Eye and Ear Infirmary Institutional Review Board (IRB): Examination of Archived Ocular Tissues for Research Studies on Ocular Structure, Function, Physiology and Association with Various Ocular Diseases, 196320-3; and the Emory Eye Center, Emory University School of Medicine IRB: Massive Retinal Gliosis, 00052749; and was conducted in compliance with the rules and regulations of the Health Insurance Portability and Accountability Act and in adherence to the Declaration of Helsinki and all federal and state laws. The files of the David G. Cogan Laboratory of Ophthalmic Pathology at the Massachusetts Eye and Ear Infirmary, and of the L.F. Montgomery Eye Pathology Laboratory at the Emory Eye Center, were retrospectively reviewed for the period 1997-2012 for cases diagnosed as retinal tumor, vasoproliferative tumor, astrocytoma, or astrocytic scar. Two cases at each institution were identified for inclusion in this study after critical review had been independently performed and agreed upon by 2 of the authors (H.E.G. and F.A.J.). Additionally, 2 neuropathologists (an author of this article [D.J.B.] and Dr Tessa Hedley-Whyte of the Neuropathology Division of the Massachusetts General Hospital) also studied the microscopic slides. Hospital records, fundus photographs, laboratory reports of fluorescein angiograms and ultrasonograms, and

office files documenting patient examinations were retrieved when available and clinical information was extracted. For comparison purposes, an enucleated globe with a retinal hemangioblastoma (von Hippel lesion) was studied with the same pathologic and immunohistochemical methods mentioned below, excluding the genetic investigations.

Paraffin-embedded microscopic sections prepared from the enucleated eyeballs were stained with hematoxylineosin, periodic acid–Schiff (PAS), and Masson trichrome stains. Immunohistochemical staining was conducted using the following probes: glial fibrillary acidic protein (GFAP) for glial cell intermediate cytoplasmic filaments; S-100 for Schwann cells; CD31 and CD34 for vascular endothelium; alpha smooth muscle actin and calponin for smooth muscle differentiation; CD163 for histiocytes; synaptophysin for evidence of synaptogenesis indicating neuronal differentiation; neurofilament for neuronal dendrites and axons; p53 for upregulation in astrocytomas; and Ki67 for cells in S-phase of DNA replication prior to mitosis. Portions of 1 tumor were fixed in 2% glutaraldehyde, processed, and transmission electron microscopy was performed (JEOL 100CX; JEOL, Tokyo, Japan). Fluorescence in situ hybridization (FISH) for the fusion gene product of KIAA1549 and BRAF was performed on 5-μm-thick paraffin-embedded tissue sections, as described elsewhere.[16,17] The methodological characterization of *IDH1*, R132H,[18] and the application of p53 to astrocytomas[19] have also been previously described. Briefly, for the astrocytic gene studies the probes for *KIAA* and *BRAF* included a fluorescein isothiocyanate (FITC)-labeled locus-specific probe RP11-355D18 (CHORI BACPAC Resources Center, Oakland, California, USA) corresponding to FITC-labeled *KIAA1549* (green) and a rhodamine-labeled locus-specific probe 726N20 corresponding to *BRAF* (red). Brain biopsy specimens were used as negative controls. Tumors were scored as positive for the *BRAF-KIAA1549* fusion when >25% of the cells demonstrated yellow signals (indicating overlap of the green and red signals), along with associated copy-number gains (at least 3 green and/or red signals) in at least 100 nonoverlapping, intact nuclei. Pyrosequencing for the activating *BRAF* V600E mutation was performed using a PyroMark W96d (Qiagen, Valencia, California, USA). A portion of the gene including codon 600 was amplified by polymerase chain reaction and then sequenced across codon 600.[17]

Results

Clinical Findings

In the present group of cases, 3 men, aged 36, 70, and 75 years, and 1 woman, aged 32 years, were affected. Each patient gave a history of either uveitis, retinal detachment surgery with scleral buckling, ocular trauma (up to 30 years earlier), or penetrating keratoplasty. The reason for enucleation was a blind, painful eye. Prior to enucleation, 2 patients were known to have an intraocular tumor; 1 of these at one time had had vision of 20/400 with an earlier diagnosis of amblyopia in the involved eye. The following brief case report exemplifies the diagnostic and therapeutic aspects of these lesions.

Case Description

A 36-year-old man was referred to a retina specialist by his general ophthalmologist for evaluation of a retinal mass associated with exudates. He complained of “waves” and a

cloudy “blob” in his right eye that he had observed for a month. There was a history of uveitis in both eyes that was first diagnosed at age 5, in addition to amblyopia in the right eye. The first visual acuities obtained by the specialist were 20/400 OD and 20/25-3 OS. Intraocular pressure was 18 mm Hg in both eyes. There was mild nuclear sclerosis and a mild posterior subcapsular cataract in the right eye, and a mild posterior subcapsular cataract in the left eye. The remainder of the anterior segment examination was unremarkable. The retinal examination of the right eye (Figure 1) revealed a pink-orange, elevated, and polypoidal lesion that was approximately 5 mm in height and 10 mm in basal diameter in the right inferotemporal far periphery. There was a surrounding shallow nonbullous retinal detachment with an exudative response that extended toward the macula and into the inferonasal periphery. There were no intraretinal telangiectasias. Retinal examination of the left eye revealed pigment epithelial dropout inferior to the center of the macula and in the inferior and nasal midperiphery as well as in the far periphery. Intravenous fluorescein angiography demonstrated early hyperfluorescence and late leakage of the lesion. Two weeks after presentation, the patient underwent cryotherapy to the base of the lesion and laser treatment to the surrounding shallow exudative retinal detachment. Although he initially reported an improvement in his visual symptoms, he subsequently developed refractory neovascular glaucoma over 16 months. After an unavailing course of intravitreal injections of bevacizumab (1.5 mg, 4 injections), the patient underwent enucleation for a blind, painful eye.

Histopathologic and Immunohistochemical Findings

The 4 enucleated globes measured between 25 × 26 × 24 mm and 20 × 24 × 18 mm. On opening the globes, the vitreous was generally cloudy and a far peripheral retinal tumor was discovered. The tumors measured at their bases and greatest heights 3.0/1.5 mm, 6.0/3.0 mm, 8.0/3.0 mm, and 5.0/7.0 mm. Low-power photomicrographs of 2 tumors illustrate their overall configuration and typical location (Figure 2, Top left and Top right). Only 1 of the lesions showed a focus of significant noninflamed bland necrosis toward its apex (Figure 2, Top right and Middle left). A rim of viable tumor was present at the very apex of this lesion bordering the vitreous cavity. There was an abrupt interface between the mummified tumor focus with its preserved, noncellular vascular outlines and the underlying viable tumor (Figure 2, Middle left). The vessels within the viable tumor and abutting the necrotic area were massively hyalinized, with very narrow lumens.

Each tumor was circumscribed but not clearly demarcated from the surrounding atrophic, mildly gliotic, and degenerate retina, with which it blended imperceptibly. The overall architecture was characterized by interweaving bundles of spindle cells and widely separated vascular channels with hyalinized walls (Figure 2, Middle right and inset). Intratumoral hemorrhage was not observed, nor were there collections of eosinophilic exudate, pigment-bearing cells, calcospherites, or dystrophic calcification. Antibodies for glial fibrillary acidic protein intensely and positively immunostained all lesions and disclosed very elongated cellular processes resulting in hair-like (pilocytic) bipolar cells (Figure 2, Bottom left). Smooth muscle actin and calponin were negative in the tumor cells but immunostained some of the vascular mural cells. Rare, mildly atypical hyperchromatic nuclei were discovered amidst the overwhelmingly bland, oval and elongated tumor cell nuclei (Figure 2, Bottom

right, top panel). Numerous CD163-positive histiocytes were scattered within the tumors but had not undergone xanthomatization; they were especially prominent in the tumor that had experienced partial necrosis.

Whereas the majority of the tumors was composed of spindle cells, in the smallest lesion a small focus of honeycombed cells with clear cytoplasm and round nuclei resembling oligodendroglial cells was detected at the posterior peripheral edge of the lesion (Figure 2, Bottom right, bottom panel). Synaptophysin and neurofilament positivity was discovered among these cells, implying that they were residual retinal elements. Eosinophilic structures within the cytoplasm of some of the tumor cells were noted (Rosenthal fibers) (Figure 3, Top left), and collections of variably sized eosinophilic granular bodies were also scattered about (Figure 3, Top right). Ki67 immunoreacted with fewer than 1% of nuclei (Figure 3, Middle left).

The walls of the hyalinized vessels were PAS-positive and Masson trichrome–positive (Figure 3, Middle right and inset). Small vessel proliferation was inconspicuous, but there were occasional clusters with moderate-sized lumens evincing incipiently thickened walls (Figure 3, Bottom left). CD31 and CD34 demonstrated a paucity of microvessels that were widely separated and lacked thickened walls (Figure 3, Bottom right). For purposes of comparison, a hemangioblastoma of the retina (von Hippel lesion) was also evaluated with CD31 and displayed a luxuriant network of capillary-sized panels, in stark contrast to their scarcity in the current tumors (Figure 4, Top left, left and right panels).

One of the more dramatic features associated with the lesions was the extent of retinal pigment epithelial proliferation, which included extensive fibrous and even osseous metaplasia (Figure 4, Top right). These phenomena were predominantly noticeable beneath and at the edges of the lesions; in 2 cases a placoid mass of fibrous metaplasia extended throughout the entire circumference of the subretinal space, almost constituting an extra tunic of the eye (Figure 4, Middle left). A narrow band of chronic inflammation was frequently detected at the base of the placoid metaplastic changes in the choroid. The retina overlying this placoid fibrous proliferation was moderately gliotic and generally did not display cystic degeneration (except for 1 microcyst with eosinophilic material immediately posterior to 1 tumor), significant intraretinal exudation, or telangiectasia.

Although there were no bullous retinal detachments with subretinal exudate, a thin lamina of exudate was discovered beneath 1 tumor. The retinas were otherwise mildly separated from the aforementioned fibrous metaplasia of the pigment epithelium. A preretinal gliotic membrane was detected focally in 3 of the 4 globes (Figure 4, Middle left). In the space between the retina and the fibrous plaque were collections of epithelioid mononucleated and multinucleated histiocytes (Figure 4, Middle left and top inset); sometimes these elements became embedded in the middle of the plaque (Figure 4, Middle left, bottom inset). The granulomatous response frequently engulfed cholesterol clefts (Figure 4, Middle right). The cytoplasms of the histiocytes were intensely PAS-positive (Figure 4, Middle right, inset). Progressively depigmenting pigment epithelial cells gradually blended into the collections of PAS-positive histiocytes (Figure 4, Middle right).

In 2 cases the choroid was moderately inflamed (1 focally, the other diffusely) with a lymphoplasmacytic infiltrate; in the others, the uvea was more lightly infiltrated (Figure 4, Middle left). An exceptional feature observed once was massive exudate of a sufficient degree to involve the choroid with collections of cholesterol clefts and xanthoma cells (Figure 4, Bottom left). In this zone there was an overlying metaplastic pigment epithelial fibrous plaque with pseudoadenomatous units (Figure 4, Bottom left and inset). Xanthoma cells were also found in this case in the retina more posteriorly, where a break in the fibrous subretinal plaque allowed a choroidal vessel to contact the outer retina (Figure 4, Bottom right). Small collections of xanthoma cells also resided between the lamellae of the sclera (Figure 4, Bottom right) and in the optic nerve head. These findings were present in the globe with the most intense vitreous exudate, illustrated in Figure 2, Top left. All lesions showed cataractous changes of the lens, peripheral anterior synechiae, and iris neovascularization. Anterior segment descemetization (new Descemet membrane deposited beneath the spread of corneal endothelial cells across the chamber angle onto the iris surface) was discovered in 1 globe. An episcleral fibrous capsule of an encircling element was observed in the case that had prior retinal detachment surgery; in another globe there was evidence of a healed posterior scleral wound.

Ultrastructural and Genetic Findings

Electron microscopic evaluation of the tumor cells in 1 case disclosed spindle shapes and myriad smaller interweaving processes (Figure 5, Top). The plasmalemmas were straight and there were no intercellular desmosomes, interdigitations, imbrications, or basement membrane deposition. The cytoplasm was endowed with numerous intermediate filaments, a few mitochondria, and short profiles of rough-surfaced endoplasmic reticulum, particularly in the perikaryon. Lysosomes were discovered in the smaller cellular processes. No smooth-surfaced endoplasmic reticulum was observed. The nuclei had clumped heterochromatin and small nucleoli with tightly wound nucleolonemas.

Immunohistochemical staining for the most frequent form of isocitrate dehydrogenase-1 (*IDH1*) mutant protein, corresponding to the R132H mutation and noted in 70%-80% of infiltrating forms of low-grade glial neoplasms,[18] did not demonstrate immunoreactivity in any of the cases. Immunohistochemistry for p53, which is commonly overexpressed in low-grade infiltrative astrocytomas,[19] was also negative in all cases. FISH for the *KIAA-BRAF* fusion event, which is noted in a high percentage of cerebellar pilocytic astrocytomas,[20] was performed in 4 cases and uncovered no fusion events in the tumors (Figure 5, Bottom). Polysomy 7 was found but was regarded as a nonspecific abnormality that does not indicate a neoplastic condition. Pyrosequencing of the *BRAF* gene for the activating *V600E* mutation, a frequent mutation in low-grade gliomas of various histopathologies, revealed no mutations in any of the 4 cases tested.[17]

Discussion

The Lesion in Our Brief Case Description, Which had the best clinical documentation, was regarded by the retinal specialist to be a “vasoproliferative tumor of the retina (VPTR),” as defined by Shields and associates in a clinical series of 103 patients.[2] Such elevated pink to

yellow lesions develop around age 40 and show no sexual or hereditary predilection. They characteristically affect the inferotemporal far periphery of the retina, with massive quantities of intraretinal and subretinal exudation.[2] Macular edema and epiretinal membranes also contribute to visual decline. Intravitreal hemorrhage from the tumor occurs in 21% of cases. In comparison with hemangioblastoma (von Hippel lesion) of the retina seen in younger individuals, the feeding and draining vessels of so-called vasoproliferative tumors are somewhat enlarged, but not to the burnished extent encountered in the von Hippel lesion. The latter entity is also responsible for considerable retinal exudate, including remote exudative involvement of the macula with intervening normal retina, whereas in the current entity the macula becomes involved as the result of the inexorable spread posteriorly by a broad front of exudate that ultimately encroaches on this structure.[21]

The lesions in the earlier series[2] were idiopathic in 74% of cases, with the remainder secondary to other conditions. Found among these latter disorders are retinitis pigmentosa, uveitis, retinopathy of prematurity, Coats disease, retinal detachment surgery, cryotherapy, accidental trauma, infections (toxoplasmosis and toxocariasis), and idiopathic inflammatory retinal diseases.[2] While typically involving the inferotemporal retinal periphery, tumors can also be detected in other locations and have rarely been noted to spread diffusely within the retina (an especially aggressive subgroup in young female subjects), and can even be multiple or bilateral.[22] There is a report of bilateral multiple lesions discovered in a pair of 58-year-old monozygotic twins, which raises the possibility of an underlying genetic abnormality in some cases.[23] The rate of tumor progression is highly unpredictable. Besides intraretinal or subretinal exudation, retinal pigment epithelial proliferation and subretinal and intraretinal blood may be detected ophthalmoscopically.[2] Some of the preceding findings differentiate the lesion from choroidal melanoma, especially the prevalent retinal exudate, which the latter does not usually exhibit.

In our series of 4 patients (3 men and 1 woman), each lesion was associated with some previous ocular insult or inflammatory disorder, but whether these events were incidental or to some degree causative is not entirely clear. When studied histopathologically, the masses were dominated by glial cell proliferations; none contained a luxuriant microvascular proliferation of endothelial cells or other vascular elements that would lead them to be designated primarily as “vasoproliferative.” Instead, the vessels seen in our cases were a small component of the lesion and were of an intermediate caliber, manifesting hyalinized walls sometimes progressing to obliteration of the lumens. They simply provided the blood supply necessary for the slow growth of the primary glial portion but had lost their ability to insulate the retinal neuroglial tissue because of loss of the blood-retina barrier function; this led to massive accumulation of exudate, which probably percolated indolently over many years. The tumors actually displayed cardinal features of a pilocytic (hair-like) astrocytoma,[24,25] which was a diagnosis that was seriously entertained for our cases by 2 experienced neuropathologists. However, in contrast to low-grade pilocytic astrocytomas of the central nervous system (CNS) and anterior visual pathways, including those of the optic nerves, which present in the first decade and trail off in the second decade (peak incidence from 8-13 years of age), our patients' average age was 53 years.

Microscopically, both CNS pilocytic astrocytomas and our retinal tumors shared the main finding of compacted bipolar cells, with slender, elongated bland nuclei and extremely elongated, interweaving gracile cytoplasmic processes (hair-like, hence pilocytic) containing intermediate cytoplasmic filaments that were GFAP-positive (fibrous astrocytes do not synthesize extracellular collagen but are so designated because of the sturdy tissue scaffolding they provide by means of their intracellular glial filaments). This pattern produces a coarsely fibrillated background matrix or neuropil appearance. Low-grade CNS pilocytic astrocytomas may display minimal nuclear atypia and few mitoses, usually little endothelial proliferation, and scant necrosis.[26] In our patients' lesions there were occasional small looser areas that corresponded somewhat to the larger myxoid foci characteristic of optic nerve pilocytic astrocytomas and that usually contain protoplasmic astrocytes (only very weakly GFAP-positive). Our smallest lesion displayed an area of honeycombed cells resembling oligodendroglial cells with their perinuclear haloes created by clear cytoplasm, a finding sometimes attributable to the collection of cytoplasmic mucin in tumor cells in true pilocytic astrocytomas.[24,25] There were also neurofilament-positive axons and synaptophysin-positive cells among the clear cells in this region, which was at the periphery of the tumor and interpreted as representing a portion of residual, entrapped retina. Mitotic figures were not observed in the current lesions, but occasional pleomorphic cells were discovered; a low Ki67 index of less than 1% was discovered, but may be up to 4% in benign pilocytic astrocytomas.[25] One lesion manifested a focus of bland infarctive necrosis at its apex with obliterative hyalinization of the vessels in the subjacent viable tissue; intratumoral hemorrhage was not found. Massive retinal gliosis that fills the vitreous cavity is probably an advanced example of the entity we are describing here,[27,28] but there has never been a case of a small tumor like ours that has been directly observed and documented over time to progress to the stage of filling the entire vitreous cavity.

Prominent vessels with thick hyalinized walls that were both PAS- and Masson trichrome–positive were regularly scattered throughout each of our lesions and were a distinctive and repetitive feature. These hyalinized vessels probably reflect inspissated transudate and were the likely source of the extensive subretinal exudate associated with the lesions. CD31 and CD34 immunostaining revealed a sparse tumor-associated microvasculature, in contrast to the rich network encountered in the retinal vascular tumors referred to as hemangioblastoma (von Hippel lesion). Eosinophilic granular bodies and Rosenthal fibers (RFs) were present, but these findings do not necessarily militate for a neoplastic diagnosis of a pilocytic astrocytoma because they can be encountered in nonneoplastic and metabolic disorders.[24,25,29] Eosinophilic granular bodies are small conglomerations of amorphous, acidophilic globules that contain alpha-1 antitrypsin, alpha-1 chymotrypsin, ubiquitin, beta-amyloid precursor protein, and alpha-crystallins, whereas RFs are eosinophilic, elongated carrot-shaped, sausage-shaped, or vermiform structures composed of degenerating intracytoplasmic clumped intermediate filament proteins, ubiquitin, small heat shock proteins HSP27, and alpha-beta crystallin.[24,25,29,30]

There was a wide variety of secondary changes throughout the eyeballs in our cases, brought about either by the tumors or possibly in part by prior inflammation, trauma, or surgery. Most conspicuous was subretinal fibrous and osseous metaplasia of the retinal pigment epithelium, seen in all 4 cases. Others have considered disturbances of the pigmented

epithelium to be intrinsic to the lesions,[8] but we regard them as a reaction to the tumors' irritative products or those derived from their leaking vasculatures. Pseudoadenomatous hyperplasia of the pigment epithelium with retention of melanin synthesis is the reason for the variable pigmentary clumping visible ophthalmoscopically (Figure 4, Bottom left). In 2 cases, fibrous metaplasia of the pigment epithelium was so extensive throughout the subretinal space but above the Bruch membrane that it formed an extra “tunic” of the eye, seen even contralaterally across the globe away from the locus of the glial tumor. This complication resembles the fibrous membrane seen in the subretinal fibrosis syndrome, including the presence of surface (subretinal) mononucleated epithelioid and giant cells.[31-33]

Additionally, 2 cases displayed subretinal cholesterol clefts with a prominent giant cell response; these histiocytes also became entrapped in the metaplastic fibrous plaques. The giant cells were intensely PAS-positive and resembled Whipple cells, probably the consequence of the ingestion of lipofuscin released from the damaged pigment epithelial cells.[34] In 1 case xanthoma cells were floridly present focally in the retina, diffusely in the subretinal space and peripheral choroid, and focally between the scleral collagenous lamellae and in the optic nerve head—in all likelihood developing from the imbibition of materials leaked from the incontinent tumor vessels. The globe showing these findings was the one with the most intense eosinophilic exudate in the vitreous and suggests that there might have been an associated hyperlipidemia, for which, unfortunately, there were no confirmatory laboratory data available. From these findings we have concluded that the ocular damage inflicted by the current tumors was caused less by the tumor itself than by the doubly damaging effects on the retina of the progressive subretinal exudation and fibrous metaplasia of the pigment epithelium.

Mild to moderate chronic choroiditis, but not retinitis, was featured in 2 cases (focal in 1 and diffuse in the second) and was negligible in the remaining 2. Shallow peripheral choroidal/ciliary body effusions were found in 2 cases but did not extend posteriorly. Intraretinal and subretinal amorphous exudates were not conspicuous except for eosinophilic material that had accumulated within 1 intraretinal macrocyst at the immediate posterior edge of a tumor. Intraretinal telangiectatic vessels that might intimate Coats disease in the presence of so much exudate were not identified; Coats disease arising in a middle-aged adult, furthermore, is a decidedly remote possibility. As already alluded to, the vitreous was opaquely eosinophilic and PAS-positive in 1 case in the absence of inflammatory cells, in keeping with fulminant exudative leakage from the sclerotic and incompetent tumor vessels. While devoid of microcysts and lakes of exudate, the gliotic retina showed severe disorganization with loss of ganglion cells (accompanied in all cases by optic atrophy), gliotic epiretinal membranes, moderate intraretinal gliosis, and the absence of photoreceptors. Some of the retinal degeneration could conceivably be secondary to the noxious microenvironment created by leaked moieties in the vitreous emanating from the tumor vessels. The iris was neovascularized, with broad peripheral anterior synechiae and angle closure in all cases; anterior segment descemetization was noted in 1 case. The foregoing substantial secondary alterations in the ocular tissues could be interpreted in aggregate as supportive of a reactive glial proliferation that had been provoked by tumor-related products.

The precise cell of origin for the current retinal lesions has not been definitively settled on a morphologic basis. The 2 prime candidates are the scattered fibrous astrocytes that insulate neuroretinal tissue at vascular interfaces and the distinctive Müller cell, which has been identified ultrastructurally in a case of retinal gemistocytic astrocytoma.[35] Müller cells are the major supporting cells within the retina, comprising approximately 90% of the retinal glial cell population and responsible for structural stability and metabolic support of the photoreceptors and other neurons.[36,37] Healthy astrocytes within the central nervous system outnumber neurons and facilitate the transfer and release of transmitter precursors, energy substrates, and hormones, and the regulation of ions and disposal of cellular waste products.[38] The cells in the current tumors were intensely positive for GFAP, indicative of a fibrous astrocytic origin. It should be noted, on the other hand, that Müller cells within the retina can be induced to participate in retinal scar formation[39] and are able to produce GFAP in response to many forms of retinal stress, including retinal detachment.[40] The results of electron microscopic studies performed on 1 of our lesions confirmed that the constituent cells were fibrous astrocytes with intermediate glial cytoplasmic filaments. They manifested straight cell borders lacking interdigitations and desmosomes; whether the source of the current tumors' cells was from transformed Müller cells nonetheless remains a moot issue.[41-43] Gemistocytic astrocytomas of the retina have displayed ultrastructural features of a Müller cell origin in the form of profiles of smooth-surfaced endoplasmic reticulum, prominent rough-surfaced endoplasmic reticulum,[35,44] and interdigitating villous processes imitative of the Müllerian fiber basket of Schultze that extends beyond the external limiting membrane;[41-43] these features, however, were not identified in our case evaluated electron microscopically. In 2 cases of massive gliosis of the retina and vitreous body, isoenzyme C of carbonic anhydrase has been detected histochemically and is regarded as a reliable marker for Müller cells.[27,28]

Rare retinal tumors known as acquired astrocytomas[44,45] and astrocytic hamartomas (or phakomas if an expression of a phakomatosis)[21] can also occur. A comparison of the current condition and these other lesions is summarized in the Table. The salient differences between acquired retinal reactive astrocytic tumor (RRAT)/VPTR and the other conditions are its onset in middle age, uncanny predilection for the pre-equatorial inferotemporal retina, and the striking degree of accompanying retinal exudate. Some confusion exists in the literature because of the tendency to use astrocytic tumor (astrocytoma) interchangeably with astrocytic hamartoma, particularly when associated with tuberous sclerosis or, much less commonly, neurofibromatosis type 1.[46] Combined hamartoma of the retina and pigment epithelium found in neurofibromatosis type 2 must be distinguished;[47] epiretinal membranes are more likely to occur in this variant of the disease.[48,49]

It is not clear whether nongelatinous, whitish lesions designated as pseudoneoplastic gliosis of the retina[21] (putatively scars) are in any way significantly different from a stationary astrocytoma. Astrocytic “hamartomas” are typically diagnosed in younger patients; syndromic tumors are frequently multiple and bilateral, situated in the postequatorial retina, and are generally clinically silent. They may appear gray, semi-translucent, and gelatinous, with poorly defined borders, or as nodular mulberry-like lesions with yellowish calcification.[50] Histopathologically, one discovers elongated fibrous astrocytes with uniform nuclei and interweaving cytoplasmic extensions. Interestingly, there is a reported case of a

VPTR associated with neurofibromatosis, but this lesion was not studied histopathologically.[51] Hamartomas have a prominent intrinsic vasculature (clinically, angiographically, and histopathologically), lack calcification initially but may acquire it[46] (some, however, can be congenitally calcified), evince prominent reactive gliosis in the adjacent retina, and are GFAP-positive.[50,52] On rare occasions such hamartomatous tumors have been documented to display rapid and aggressive growth and display cells with atypical nuclei.[50,52]

The foregoing findings have led some authorities to conclude that the subset of acquired and nonsyndromic retinal astrocytomas with feeder vessels is composed of true, low-grade neoplasms;[35,44,45,50,52] these are best exemplified by giant cell astrocytic tumors typically but not always encountered in tuberous sclerosis that are more aggressive in their behavior.[53,54] We doubt that they are closely related to the present entity under discussion. A new category of presumed solitary circumscribed retinal astrocytic proliferation (PSCRAP) has recently been described as a benign, elegantly demarcated, abruptly elevated, stationary lesion. PSCRAP appears white and opaque, is less than 2 mm elevated, and is located in the inner sensory retina, where it obscures traversing vessels of the posterior arcades. It lacks feeder vessels and adjacent gliosis and does not exhibit calcification, subretinal fluid, or exudate.[55] Of 7 lesions, 1 eventually and inexplicably disappeared spontaneously. These lesions have not yet been studied histopathologically and are definitely in need of further investigation to determine if they warrant a separate diagnostic category. At present they seem to be a variant of acquired astrocytoma with arrested growth. PSCRAP has been likened to an inner retinal glial nodule with mitoses discovered incidentally in an enucleated globe,[56] which paradoxically would imply the capacity for ongoing growth. Our lesions, however, do not resemble PSCRAP based on their clinical behavior.

Given the cytologic similarity of our lesions to CNS pilocytic astrocytomas, including the presence of Rosenthal fibers and eosinophilic granular bodies, we pursued further genetic testing to determine whether the lesions were indeed related. Immunohistochemical stains for the mutant form of *IDH1* (R132H) and p53 upregulation and overexpression are characteristically positive in CNS low-grade infiltrative astrocytomas,[18,19] but were negative in our cases. Additionally, no KIAA-BRAF fusion gene products were tested with FISH and no activating mutations of *BRAF* (V600E) were noted. KIAA-BRAF fusions have been detected in a large percentage of cerebellar pilocytic astrocytomas and *BRAF* mutations are found in a variety of lower-grade gliomas, including pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and ganglioglioma.[17,20,57,58] BRAF is a serine-threonine–specific protein kinase in the MAPK pathway that leads to downstream activation of ERK, a kinase involved in cell-cycle progression. High rates of spontaneous mutations of the gene encoding for cytosolic nicotinamide adenine dinucleotide phosphate (NADP+)-dependent IDH1 have been reported in pilocytic astrocytomas. An antibody specific for heterozygous point mutation of *IDH1* codon 132 IDH1R132H has been identified as having high sensitivity and specificity in the pilocytic astrocytomas. As a cautionary note, one should add that it is possible that the genetic mutations responsible for generating low-grade astrocytomas in the retina may be different from those elsewhere in the CNS. Taken

together, however, the preponderance of evidence supports the inference that the retinal glial tumors in our cases are not astrocytic neoplasms, but rather reactive glial proliferations.[17]

RRAT is probably one of a limited number of responses that the retina is capable of mounting to various kinds of injuries. Some studies have shown that adult CNS astrocytes may become proliferative in response to certain types of injury and generate Rosenthal fibers.[59] Conceivably, the astrocytic lesions that we have observed in the retina could represent a reaction to prior retinal insult. Massive gliosis of the retina and vitreous has been reported bilaterally in an infant with retinopathy of prematurity[60] and an investigation of a case of massive retinal gliosis in a female patient with a microphthalmic eye revealed that the gliotic mass contained multiple clones determined by the HUMARA methodology (human androgen receptor gene assay for clonality utilizing X chromosome inactivation in female subjects), findings in both cases that are consistent with a reactive proliferation.[28] The association of many “vasoproliferative tumors” of the retina with other ocular diseases such as uveitis (as in our index case), retinal detachment, retinopathy of prematurity, Coats disease, and trauma has led other investigators to suggest that these tumors may form as a reactive process to an antecedent insult.[22] The idiopathic lesions described by Shields and associates,[2] as well as by others, may actually have formed in the wake of a subclinical or cryptic event that was never reported or was forgotten by the patient, or a prior episode of mild inflammation that went untreated.[2]

Our cases therefore confirm the preliminary conclusion contained in a few earlier reports in the literature that the clinical entity VPTR is actually an astrocytic (glial) proliferation.[8,13,14] The term “reactionary retinal glioangiosis” has been proposed as a more appropriate term than “vasoproliferative tumor,” but it still conveys the impression that blood vessels are the major or primary component.[14,15,60,61] We would instead suggest further refining the diagnostic rubric to “retinal reactive astrocytic tumor” (RRAT), since the vascular portion of the tumor appears to be merely supportive and the genetic studies do not unequivocally support an autonomous neoplasm. The modifier “astrocytic” is preferable to “glial” because the latter term is more generic and subsumes oligodendroglia and microglia (macrophages) as well as astroglia. Further studies to better define the cell types involved (fibrous astrocytes vs Müller cells that acquire glial filaments), and to more completely characterize these proliferations as reactive and polyclonal,[27,28] would be essential for advancing our understanding of this disease spectrum.

For completeness, a comparatively remote possibility needs to be addressed. In spite of the results of the genetic studies performed on the astrocytic component, the current lesions might nonetheless still be vascular in nature, but with the passage of time and progressive growth the recruitment of reactive fibrous astrocytes results in a dilution of the microvascularity. Two vascular components were identified: widely spaced sclerotic nutrient channels such as one sees in nonvasogenic astrocytomas[25] and peripheral nerve schwannomas,[62] and a background capillarity. Von Hippel retinal lesions, which are profusely vascular, retain a prominent capillary component even in advanced stages when there has been an exuberant accumulation of lipidized interstitial cells (Figure 4, Top left).[62] The capillary component, however, was remarkably inconspicuous in all of the present lesions, requiring immunohistochemical probes CD31 and CD34 for its identification, and

was equally sparse in the smallest lesion (1.5 mm in elevation) and the largest (7 mm in elevation). It is thus highly improbable that an expanding population of astrocytes hypothetically crowded out or nearly obliterated what was fundamentally a vascular tumor.

There is no standard approach to the management of reactive astrocytic tumors of the retina, a reflection on their uncommon presentation and the absence of an agreed-upon preferred and efficacious therapy.[22] Cases that are slowly progressive with minimal vascular leakage probably can be handled with observation alone.[2] Lesions that are large or sight-threatening because of exudation have been treated with a variety of methods, including intravitreal anti–vascular endothelial growth factor agents,[63] transconjunctival cryotherapy with a standard triple freeze-thaw cycle,[2] photodynamic therapy with verteporfin,[64,65] and plaque radiation using iodine-125[66] or ruthenium-106.[67] Surgical resection,[68-70] either transscleral or transvitreal, or pars plana vitrectomy with endolaser have also been attempted. Surgical resection allows for a tissue diagnosis, should this be in question. Given the reactive nature of these lesions, their unpredictable behavior, and frequent benign course, observation is a reasonable choice for lesions that are small and non-sight-threatening. Recent rate of growth, however, should be given weight in deciding when to intervene if a formerly stationary lesion becomes activated. Our index patient experienced a growth of his tumor from 5 to 7 mm in height over a 2-year period, during which various therapies were unavailing and exudate continued to develop. Choice of therapy should be additionally dependent on the degree of vision loss, location of the lesion, and overall health of the patient. Surgical resection should be the subject of further study for a distinct subset of patients with unrelenting centrifugal spread of exudate toward the macula. This recommendation is reinforced by the histopathologic findings. The major attacks on retinal functional survival appear to stem from the presence of subretinal histiocytes and lipidic material, and from pigment epithelial fibrous metaplasia even at a considerable distance from the lesion itself.

Acknowledgments

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Biography

After serving as Chief Resident at the Massachusetts Eye and Ear Infirmary, Dr. Lynn Perry performed a fellowship in Ophthalmic Pathology in the David G. Cogan Eye Pathology Laboratory under the preceptorship of Dr. Frederick Jakobiec and was partially supported by the Heed Foundation. Her clinical interests include complicated cataract surgery, eye trauma and ocular pathology. Currently, she is an assistant professor in the Ophthalmology Department at Storm Eye Institute, Medical University of South Carolina.

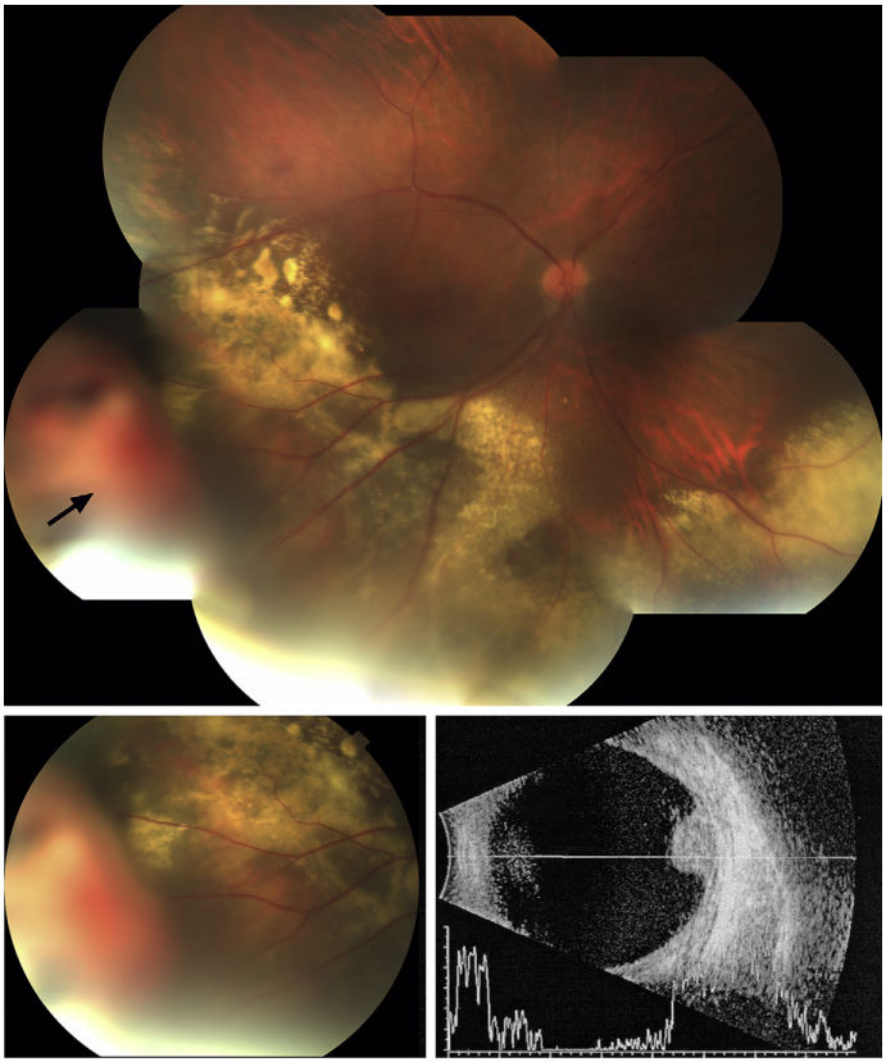

Figure 1.

Clinical features of reactive retinal astrocytic tumor. (Top) Photomontage of right fundus: appearance of an elevated lesion in the far retinal periphery (arrow) with extensive surrounding exudate including in the inferonasal quadrant. Note that there are no large feeding and draining vessels, in contrast to a von Hippel lesion (hemangioblastoma). (Bottom left) Somewhat blurred view (due to difficulty in focusing on peripheral lesion) of pink-yellow to orange retinal lesion toward the left. (Bottom right) B-scan ultrasonogram displays a well-circumscribed retinal mass that measured5 mm in elevation without choroidal or scleral acoustic excavation. The superimposed A-mode ultrasonogram shows moderate and uniform intralesional internal acoustic reflectivity without spikes that might suggest calcification.

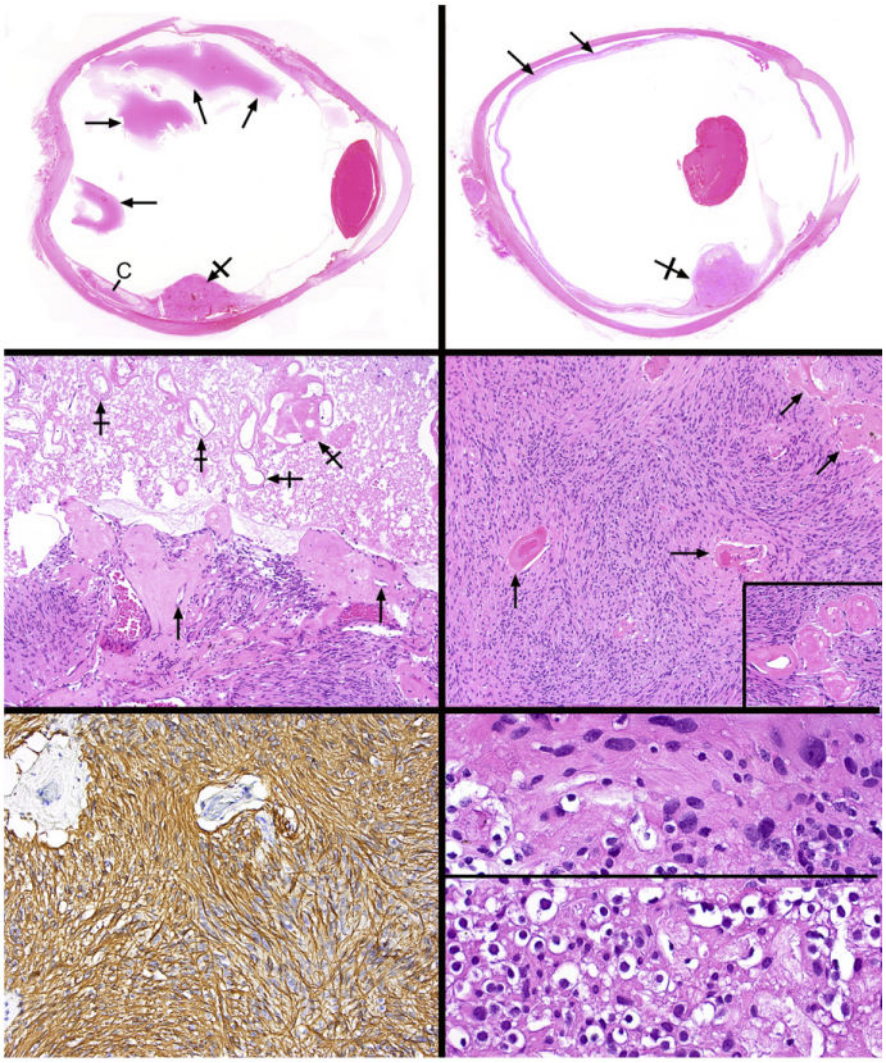

Figure 2.

Histopathologic features of reactive retinal astrocytic tumors. (Top left) Enucleated globe containing inferotemporal moderately elevated tumor (crossed arrow) with eosinophilic exudate present in the vitreous cavity (arrows). A large intraretinal cyst (C) is present immediately posterior to the mass. (Top right) Another example of a reactive astrocytic tumor (crossed arrow) with an area of apical necrosis. Contralateral to the tumor is an area of diffuse placoid fibrous thickening in the subretinal space (arrows) corresponding to areas of metaplasia of the retinal pigment epithelium. (Middle left) There is no inflammation within the necrotic area of the tumor present in the top right panel. Ghost-like vascular outlines (crossed arrows) are clearly identifiable. At the bottom is the interface with viable tumor showing massively sclerotic vessels with barely discernible lumens (arrows). (Middle right) All of the tumors were composed of interweaving bundles of bipolar spindle cells with regularly spaced sclerotic vessels (arrows), shown in a small cluster in the inset. (Bottom left) Glial fibrillary acidic protein (GFAP) intensely and diffusely immunostains the highly elongated (pilocytic) fibrous astrocytes composing the lesions. (Bottom right) Top panel: Two of the lesions displayed cells with mildly atypical nuclei consisting of hypochromasia,

more rounded than elongated nuclear forms, and occasional nucleoli. Bottom panel: In 1 tumor there was an area at the periphery abutting the adjacent retina with honeycombed cells having clear cytoplasm and resembling oligodendroglial cells. Some of these cells were synaptophysin- and neurofilament-positive, indicating that they were probably persistent entrapped elements of the preexisting retina being replaced by the tumor. (Top left and Top right, hematoxylineosin [H&E], ×7; Middle left, H&E, ×7; Middle right, H&E, ×100, inset ×100; Bottom left, immunoperoxidase reaction, diaminobenzidine chromogen, ×200; Bottom right, H&E, top panel ×500, bottom panel ×400.)

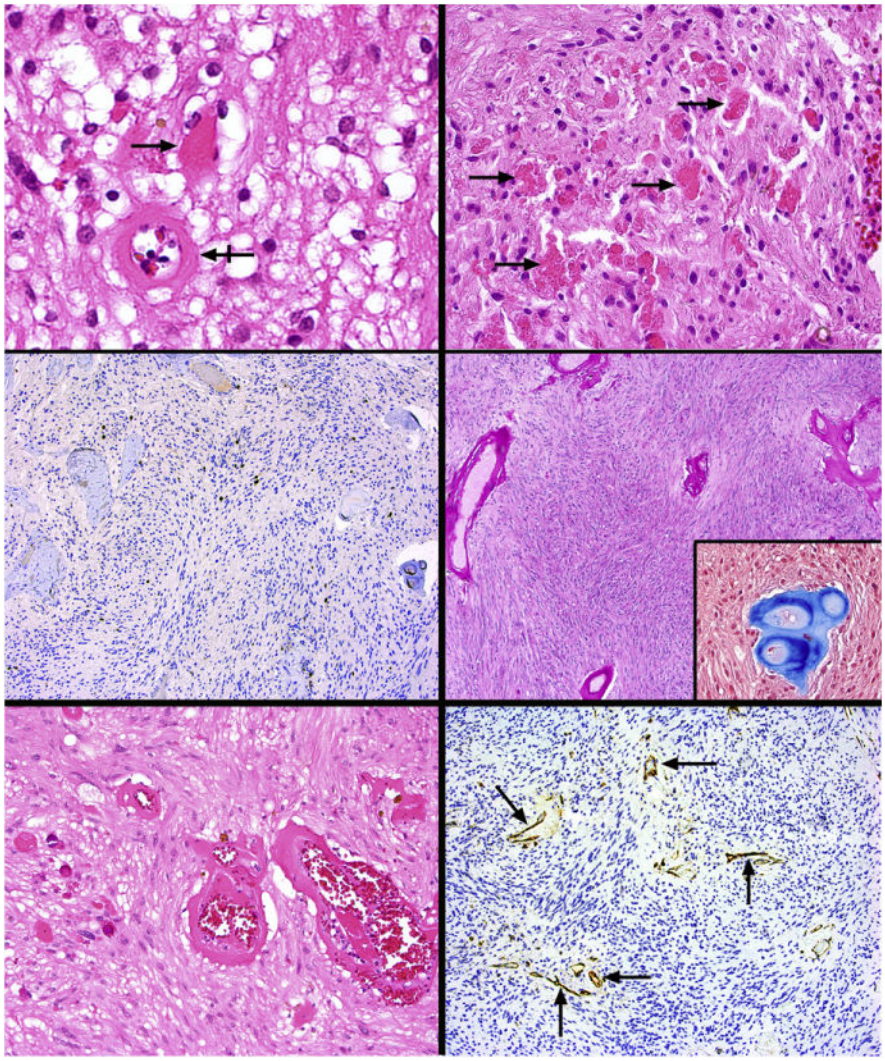

Figure 3.

Histopathologic figures of reactive retinal astrocytic tumors. (Top left) A homogeneous eosinophilic intracytoplasmic inclusion (arrow), called a Rosenthal fiber, is present in this more loosely textured field. The crossed arrow indicates a mildly sclerotic blood vessel. (Top right) Numerous collections of eosinophilic granular bodies (arrows) are distributed among the astrocytic cells. (Middle left) Ki67 stains a minimal number of cells (fewer than 1%) within the tumors. (Middle right) The tumors feature widely spaced sclerotic vessels, which are endowed with periodic acid–Schiff (PAS)-positive, thickened walls. The inset depicts the trichrome positivity signifying collagen in the vascular walls. (Bottom left) Rare cluster of proliferating blood vessels within the tumors. Note the eosinophilic granular bodies on the left. (Bottom right) CD31 immunostains a sparsity of microvessels within the tumor (arrows). (Top left, hematoxylineosin [H&E], ×500; Top right, H&E, ×400; Middle left, immunoperoxidase reaction, diaminobenzidine chromogen, ×100; Middle right, PAS, ×100, inset, Masson trichrome, ×200; Bottom left, H&E, ×400; Bottom right, immunoperoxidase reaction, ×100.)

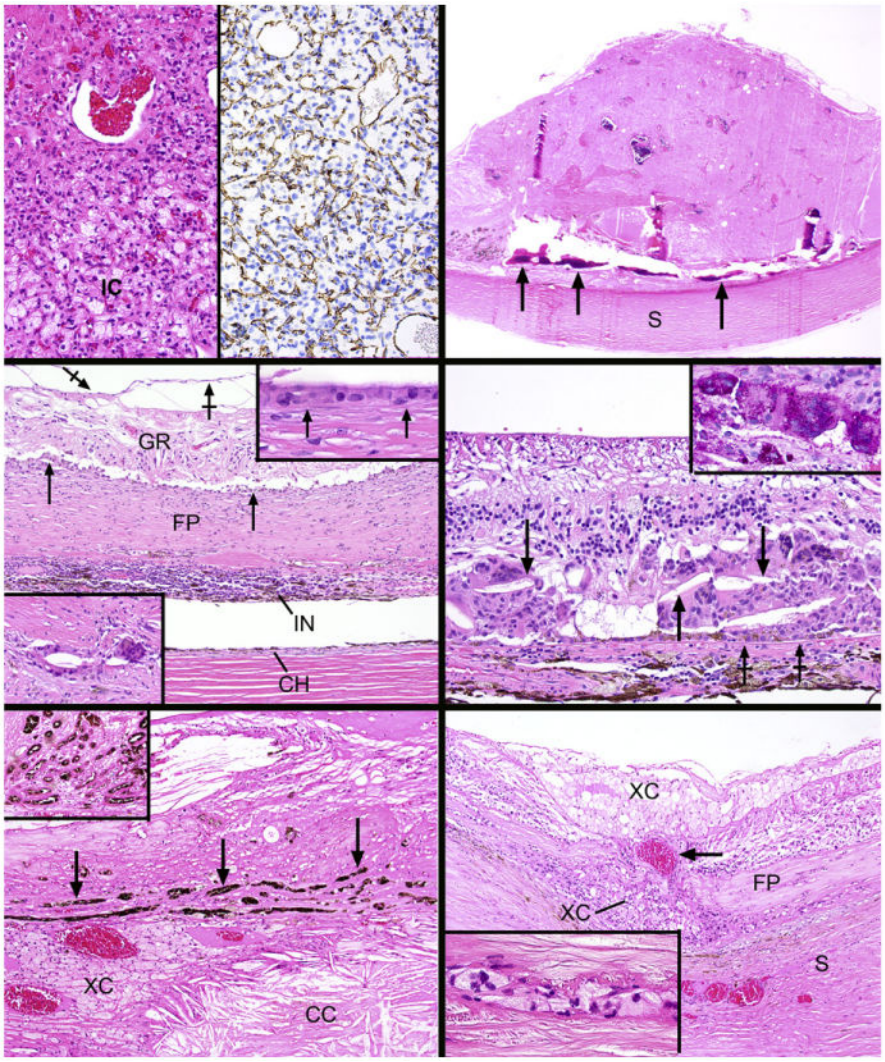

Figure 4.

Histopathologic features of reactive retinal astrocytic tumors. (Top left) The left panel illustrates a hemangioblastoma (von Hippel lesion) with lipidized interstitial cells (IC). The right panel shows CD31 immunostaining of a rich background microvasculature, in contrast to the minimal microvasculature of reactive retinal glial astrocytic tumors (see Figure 3, Bottom right). (Top right) Osseous metaplasia of the retinal pigment epithelium (arrows) underlies a reactive astrocytic tumor (S, sclera). (Middle left) Diffuse placoid fibrous metaplasia of the retinal pigment epithelium in a zone contralateral to where the astrocytic tumor was located. On the surface of the fibrous plaque (FP) is a layer of loosely adherent histiocytic cells (arrows). The overlying retina shows a preretinal gliotic membrane (closed arrows), disorganization, loss of ganglionic and photoreceptor cells, and mild intraretinal gliosis. The underlying choroid exhibits a moderately intense lymphocytic infiltrate (IN). The inset in the upper right demonstrates a monolayer of epithelioid histiocytes (arrows) on the surface of the fibrous plaque. The inset on the bottom left demonstrates entrapped multi-nucleated and mononucleated epithelioid histiocytes within the plaque. (Middle right) There are myriad mononucleated and multi-nucleated granulomatous cells in the subretinal space

above the pigment epithelium (crossed arrows) engulfing cholesterol clefts (arrows). The inset displays intense periodic acid–Schiff (PAS) positivity in the cytoplasm of the histiocytes, mimicking the appearance of Whipple cells. (Bottom left) Pseudoadenomatous proliferation where the pigment epithelium (arrows and inset) begins to undergo metaplasia into a fibrous plague. In the choroid there are masses of cholesterol clefts (C) and a collection of fully lipidized xanthoma cells (XC). (Bottom right) A blood vessel is present in the deep retina (arrow), having originated from the choroid and migrated through a break in the metaplastic fibrous plaque (FP). The vessel is surrounded by xanthoma cells (XC), which are also present in the retina above. (S, sclera.) The inset displays intralamellar histiocytes within the sclera. (Top left, left panel, hematoxylineosin [H&E], ×200, right panel, immunoperoxidase reaction, diaminobenzidine chromogen, ×200; Top right, H&E, ×20; Middle left, H&E, ×100, insets ×200 and ×400; Middle right, H&E, ×200, inset, PAS, ×400; Bottom left, H&E, ×100, inset ×100; Bottom right, H&E, ×100, inset ×400.)

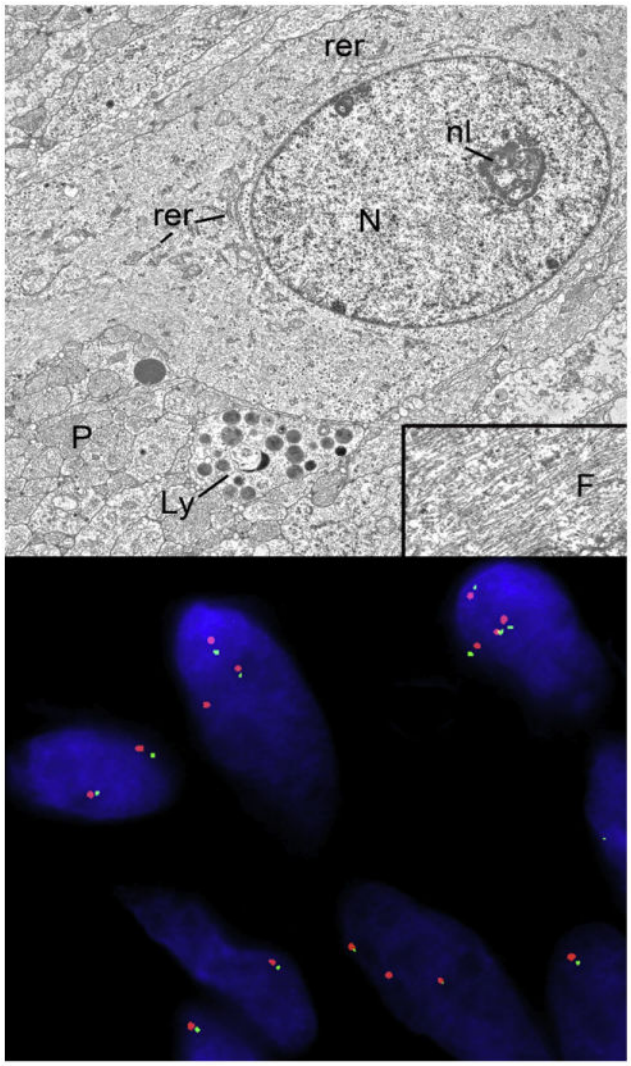

Figure 5.

Ultrastructural and genetic features of reactive retinal astrocytic tumors. (Top) Transmission electron micrograph of a tumor cell reveals short profiles of rough-surfaced endoplasmic reticulum (rer) in the perikaryon region. The cell has straight borders without basement membranes. Adjacent small cellular processes (P), some of which contain lysosomes (Ly), are clustered toward the bottom left and upper left. The inset highlights intermediate cytoplasmic filaments that correspond to the glial fibrillary acid protein positivity of the tumor cells. There are no villous processes suggestive of Müller cells. (Bottom) Fluorescence in situ hybridization analysis failed to reveal a *BRAF-KIAA* fusion because probes *BRAF* (red) and *KIAA* (green) were nonoverlapping. (Top, ×11 000, inset ×15 000; Bottom, ×1000.)

Table
Differential Diagnosis of Retinal Astrocytic Tumors

Diagnosis	Clinical Features	Pathologic Features	Positive Immunohistochemical Biomarkers	Genetic Findings
Reactive retinal astrocytic tumor (vasoproliferative tumor of the retina)[a]	Pre-equatorial, inferotemporal pink-yellow-orange mass; prominent feeder vessel absent; discovered around age 40; abundant exudate; shallow, nonbullous retinal detachment initially surrounding lesion, then spreading farther afield	Hair-like (pilocytic) spindle-shaped fibrous astrocytes; may contain Rosenthal fibers and granular bodies; modest number of sclerotic vascular channels; few capillaries; far-reaching subretinal exudate, cholesterol clefts, and granulomatous response; extensive fibrous metaplasia of pigment epithelium	GFAP, S100	Nonsyndromic and no mutations
Massive reactive retinal gliosis	Non-pigmented mass filling half to all of vitreous cavity; extreme form of reactive astrocytic tumor	Spindle and polygonal cells; Thickened calcospherites; Rosenthal fibers; Mueller cell origin	GFAP, S100. isozyme C of carbonic anhydrase	Nonsyndromic, following ocular insult
Pilocytic astrocytoma[a]	Not reported to date in retina; occurs as an optic nerve tumor of children; generally seen in first decade in neurofibromatosis-1	Hair-like (pilocytic) spindle-shaped fibrous astrocytes; prominent Rosenthal fibers and granular bodies; scattered sclerotic vascular channels; microcysts	GFAP, S100, α-β crystallin, alpha-1 antitrypsin and chymotrypsin	*IDH1R132H* and *BRAF*; V600E mutation; neurofibromatosis-1 gene
Astrocytoma	Yellowish, solitary, well demarcated, with modest feeder vessel; acquired, slowly progressive lesions in adults; <6 mm in thickness; retinal exudate and surrounding subretinal fluid; late nonbullous retinal detachment; rare vitreous hemorrhage	Spindled fibrous astrocytes	GFAP, S100	Isolated, nonsyndromic
Giant cell (gemistocytic) astrocytoma[b]	Posterior pole exophytic fleshy mass; tuberous sclerosis but occasionally isolated; usually less than age 10, but occasionally in middle age; progressive and aggressive growth; hemorrhage; intraretinal exudate and retinal detachment	Large, eosinophilic, glassy, polygonal, bloated or stuffed (gemistocytic) astrocytes;[c] necrosis and calcification (calcospherites)	GFAP, S100, neuron-specific enolase	TSC locus heterogeneity
Astrocytic hamartoma (phakoma)[d]	Translucent, gelatinous mass; yellowish, calcified mulberry or tapioca lesions also well recognized; no feeder vessels; rare exudate and surrounding	Spindle-shaped fibrous astrocytes and less commonly a few giant scattered astrocytes; can be abundant calcific deposits	GFAP, S100	TSC locus heterogeneity; neurofibromatosis-1 and -2 (if combined hamartoma) genes; specific retinitis pigmentosa mutation when relevant

Diagnosis	Clinical Features	Pathologic Features	Positive Immunohistochemical Biomarkers	Genetic Findings
	subretinal fluid; congenital and first decade; stationary or slow, minimal enlargement; usually seen in tuberous sclerosis (may be multiple) and much less frequently in neurofibromatosis-1 and retinitis pigmentosa; different from a combined hamartoma of retina and pigment epithelium in neurofibromatosis-2			
Presumed solitary circumscribed retinal astrocytic proliferation[e]	Circumscribed, whitish, small stationary, abruptly elevated lesion (<2 mm); autofluorescence; around 50 years old; inner retinal involvement that obscures traversing retinal vessels; no feeder vessels; no exudate, calcification, or surrounding subretinal fluid	Assumed to be a glial nodule of nerve fiber layer; no direct pathology available but may have mixture of ovoid and spindle cells found in related pathology	Presumably GFAP and S100	Nonsyndromic; no mutations known
Hemangioblastoma (von Hippel lesion)	Pink mass typically found in von Hippel–Lindau disease around age 18; isolated lesions at age 36; optic disc or peripheral retinal locations; prominent dilated and tortuous feeder and draining vessels; abundant intraretinal exudate and eventual retinal detachment	Interstitial vacuolated ovoid cells with luxuriant permeating capillary plexus; intraretinal exudate and exudative detachment	GFAP, S100, neuron-specific enolase	VHL gene mutation

GFAP = glial fibrillary acidic protein; TSC = tuberous sclerosis complex.

[a] The light microscopic appearance of reactive retinal astrocytic tumors bears a striking resemblance to that of central nervous system pilocytic astrocytomas but lack the latter's genetic abnormalities.

[b] Giant cell astrocytomas are often destructive of the eyeball but nonmetastasizing.

[c] Giant cells as a minimal subset may occasionally be observed in small, slowly enlarging nonaggressive tumors.

[d] Distinguishing between an astrocytic hamartoma (phakoma) and a small astrocytoma can be somewhat blurred and arbitrary; the former is generally, but not always, stationary, while the latter displays progressive growth but at variable rates. Astrocytic hamartomas are congenital cellular malformations or birthmarks, whereas astrocytomas are acquired and presumably true neoplasms of adults.

[e] May be an arrested, small, isolated astrocytoma of adults.