Retinal Vasoproliferative Tumors

Surgical Management and Histological Findings

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Vascular masses occurring in the peripheral retina have been described extensively in the literature. Many terms, including “presumed acquired hemangiomas,” “hemangioma-like,” “angiomatous masses,” “angioma-like,” “peripheral retinal telangiectasis,” and “vasoproliferative tumors,” have been suggested that reflect the lack of the known histological features and the potentially variable causes. We describe the histological features of 2 patients who underwent transcleral local resection as management for suspected choroidal melanoma. Pathological examination of these tumors reveals the constituents to be primarily benign glial cell proliferation with secondary vasoproliferation. The weight of the literature agrees with a reactionary process. We therefore suggest the term “reactionary retinal glioangiosis.” Transcleral resection has a place where diagnosis is difficult. It prevents an unnecessary enucleation and allows accurate tissue diagnosis.

In 1983 Shields et al1 coined the term “presumed acquired retinal hemangiomas” to describe solitary peripheral retinal vascular masses that resembled either retinal hemangiomas or choroidal melanomas. The initial study was in a small group of patients, but a later review of a larger group of 103 patients by Shields et al2 led to a change in nomenclature, with the authors renaming these lesions “vasoproliferative retinal tumors.” They proposed a classification based entirely on clinical features. These studies were not supported by histopathological features although Welch,3 in discussion of the 1983 paper by Shields et al,1 suggested that these tumors might be similar to lesions described in 1966 by Henkind and Morgan4 in 4 enucleated eyes.

Since morphological descriptions of this clinical entity are therefore sparse, we describe the pathological features of 2 tumors that conform to the clinical descriptions provided by Shields and coworkers.1,2 The patients were referred to the Scottish National Ocular Oncology Service, Glasgow, for the treatment of suspected malignant melanomas of the peripheral choroid. The differential diagnosis of these cases included vasoproliferative retinal tumors; however, since the diagnosis of malignant melanoma could not be excluded, the tumors were removed by transcleral resection. In this article we describe the clinical and histopathological features of these rare benign abnormalities.

REPORT OF CASES

CASE 1

A 61-year-old man was referred in September 1997 with the diagnosis of a presumed choroidal melanoma in the inferotemporal quadrant of the right eye. Five months previously he had noticed distortion and decreased vision in this eye. On ophthalmic examination visual acuity was reduced to counting fingers OD and 20/20 (6/6) OS. There was a right afferent pupil defect. Funduscopy revealed a solid-looking lesion in the inferotemporal quadrant of the right eye with associated exudative retinal detachment and retinal hemorrhage (Figure 1). No obvious feeder or draining vessels were noted. A definite transillumination defect associated with the lesion was noted. Fundus fluorescein angiography showed late hyperfluorescence only. Ultrasound B-scan

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demonstrated a 6.3 × 5.6-mm choroidal mass that showed moderate to high internal reflectivity with associated retinal detachment; the images were consistent with a choroidal melanoma (Figure 2). Results of systemic investigations were normal; there was no family history of ocular disease. The patient was not hypertensive.

Although the clinical appearance was not entirely typical of a choroidal melanoma, this diagnosis could not be excluded and a decision was made to locally resect the mass and apply a radioactive ruthenium 106 plaque over the resection site.

Preoperatively the tumor did not involve the choroid as evidenced by the lack of adhesion between the scleral trapdoor and an apparently normal choroid. The diagnosis of choroidal melanoma was therefore immediately in doubt. The tumor was excised as planned because the aim was to preserve vision and the procedure was completed by the technique described below in the “Transcleral Resection” subsection of the “Materials and Method” section.

Because the initial histological examination revealed a vasoproliferative tumor with no evidence of malignancy, the ruthenium 106 plaque was removed 2 days postoperatively. Since similar lesions are found in von Hippel-Lindau syndrome, appropriate investigations were carried out and the results were normal.

At follow-up assessment 4 months postoperatively, although visual acuity was restricted to hand movements, subjectively the patient felt there had been a noticeable improvement. The retina had anatomically flattened, the vitreous was much clearer, and a marked resolution of the retinal vascular reaction was noted (Figure 3). The patient remains stable at 18 months’ follow-up.

CASE 2

A 63-year-old man was referred in November 1998 with a right inferonasal raised mass presumed to be a choroidal melanoma. He had noticed gradual reduction of vision in this eye. On ophthalmic examination visual acuity was 20/130 (6/36) OD and 20/20 (6/9) OS. Funduscopy revealed a yellow crystalline inferonasal mass with associated exudative retinopathy (Figure 4). No obvious feeder or draining vessels were noted. Ultrasound B-scan confirmed a solid lesion 10 mm across the base and 5 mm in depth with associated vitreous debris consistent with a choroidal melanoma (Figure 5). Fluorescein angiography was not performed. Results of systemic investigations were normal; there was no family history of ocular disease.

Local resection surgery with brachytherapy was planned and carried out as described below in the “Transcleral Resection” subsection of the “Materials and Method” section. Again, preoperatively no choroidal or scleral involvement was found, putting the initial diagnosis in question. The surgical procedure was completed without complication. The ruthenium 106 plaque
was removed 3 days postoperatively once the pathological diagnosis was provided and confirmed that there was no evidence of malignancy.

At the 1-month follow-up visual acuity remains 20/130 (6/36) OD and the retina remains flat (Figure 6). The patient remains stable at 6 months’ follow-up.

**MATERIALS AND METHODS**

**TRANSCLERAL RESECTION**

The surgical approach of transcleral local resection involves localization of the tumor by indirect ophthalmoscopy followed by formation of a lamellar scleral flap. The tumor is then dissected from the retina and excised along with the deep scleral lamella and an area of normal surrounding choroid, avoiding retinal damage. The scleral flap is replaced and sutured in position. Intravitreal sulphurhexafluoride is injected to provide retinal tamponade. Hypotensive anesthesia with the systolic blood pressure being lowered to around 50 mm Hg is obligatory.5,6

**PATHOLOGICAL FEATURES**

The excised retinal mass, the attached choroid, and the inner scleral flap in both cases were fixed in buffered 2.5% glutaraldehyde and processed for paraffin histological examination.

Paraffin sections were stained with a variety of routine stains including hematoxylin-eosin, periodic acid-Schiff, trichromes (Mallory, Masson, or picro-Mallory), reticulin, Martius scarlet blue, and the elastica van Gieson. Immunohistochemical markers were used to identify the glial component (glial fibrillary acidic protein, S100 protein, and neurofilaments) and the endothelial cells (QB10) in the blood vessels within the tumor.

**RESULTS**

**CASE 1**

Macroscopically the mass measured 7 × 4 × 3 mm and consisted of soft-folded, pale brown hemorrhagic tissue.

Microscopic examination demonstrated that the tumor consisted of a large mass of spindle cells surrounding blood vessels of various sizes (Figure 7, A-D). The spindle cells were of uniform size and mitotic figures were absent: positive staining with phosphotungstic hematoxylin and glial fibrillary acidic protein confirmed the glial nature of these cells (Figure 7, D). In
1 paraffin block, a large mass of fibrin and granulation tissue was identified (Figure 7, B). The major part of the vascular component took the form of clusters of channels lined by plump endothelial cells, within hyalinized connective tissue (Figure 7, B and D). Small angiomatoid capillary clusters were also present (Figure 7, C) within gliotic areas and at the periphery of the mass. Fibrinous, lipid, and serous exudates were present in the tissue adjacent to the blood vessels. Extensive areas of “basement membrane deposit” (synonyms: basal linear deposit, basal lamina deposit) were present on the inner surface of Bruch’s membrane (Figure 7, E). Elsewhere Bruch’s membrane was lined by a fibrotic membrane due to proliferation and metaplastic change within the retinal pigment epithelium (RPE) (Figure 7, F). A few foci of neovascularization were noted in this region (Figure 7, F). Retinal tissue containing hemorrhage and exudates was identified at 1 periphery. Abnormal tissue extended to the edge of the mass in most paraffin blocks.

CASE 2

Macroscopically a tan lobulated mass (Figure 8, A) was attached to a flatter region in which there were pale yellow crystalline areas. The total dimensions of the mass were $6 \times 5 \times 3$ mm. Blood vessels were prominent on the surface of the mass.

On microscopic examination the main mass of the tumor was formed by spindle cells in an irregular arrangement (Figure 8, B-D). Cystic spaces surrounded by macrophages were identified in the flatter region; these corresponded to the yellow loci shown in Figure 8, A. Blood vessels within the tumor were frequently associated with a perivascular lymphocytic infiltration and this was associated with the high endothelial venule phenomenon. Examples of thrombosis and intraluminal endothelial cell proliferation and fibrin deposition were identified; many blood vessels were hyalinized and deposits of fibrin were plentiful in the inner part of the tumor (Figure 8, C and E). A feature of interest was a focus of RPE proliferation within the glial mass (Figure 8, F) These appearances were consistent with a peripheral retinal vascular tumor. In this case the tumor tissue extended to the exfoliation.

Vascular masses occurring in the peripheral retina have been described clinically using many terms including “presumed acquired retinal hemangiomas,” “hemangioma-like,” “angiomatous masses,” “angioma-like,” “peripheral retinal telangiectasia,” and “vasoproliferative tumors.” The reason for the varied descriptive terms reflects the lack of the known histological features and the potentially variable causes.

Capillary hemangiomas of von Hippel-Lindau syndrome are included in the differential diagnosis. Such hamartomas usually have characteristic features of occurring (1) in younger patients, (2) as multiple tumors, (3) bilaterally, (4) with dilated feeder and draining vessels, (5) localized anywhere in the retina, and (6) in patients with the stigmata of von Hippel-Lindau syndrome including a positive family history of ocular disease.

Shields et al reclassified vasoproliferative retinal tumors as primary or secondary. Primary tumors according to their classification are characteristically unilateral, solitary lesions with normal feeder and draining vessels, occurring most commonly in the inferotemporal quadrant of the fundus. Other authors have also noted the inferior location as is the case in our patients. Patients considered to have primary tumors do not have a family history of ocular disease, are middle-aged or elderly, and are systematically well. Fifty percent of these patients suffered from mild hypertension. Therefore, our cases could be regarded as primary tumors.

Secondary tumors have been associated with many ocular conditions including retinitis pigmentosa, retinopathy of prematurity, retrolental fibroplasia, retinal detachment surgery, and Coats’ disease. Such tumors tend to be smaller lesions and have associated areas of RPE proliferation. None of the above-noted features were relevant to the present cases.

Subsequent to classification by Shields et al, Khawly et al have described a case of acquired vasoproliferation that they suggested might be caused by reactive astrocytic hyperplasia, which they treated with photocoagulation. Many similar cases in the literature have been managed by observation, although some have been treated with photocoagulation or cryopexy with indifferent results. Some pathological examples of vasoglia proliferation were found incidentally in eyes enucleated for complicated disease and, in 1979, Berger et al reported similar histological features noted in our patients following local resection for a presumed malignant melanoma, but this tumor was classified as “massive retinal gliosis.”

It could be argued that the prominent glial component would justify a classification of massive retinal gliosis and the histological features of our patients are similar to those described and classified by Berger et al. The frequently cited paper by Henkind and Morgan describes variable pathological changes in 4 eyes, but their case 1 has many similarities to our specimens. Because the weight of evidence in the literature supports the hypothesis that this pattern of pathology is reactionary, it is highly likely that the proliferation of the RPE seen in both of these specimens is also reactionary, secondary to a stimulus of unknown nature.

It is appropriate to mention that amelanotic tumors of the RPE could be considered in the differential diagnosis. Such tumors show considerable clinical variation; however, their clinical appearance can be
similar to vascular tumors, as described by Shields et al.17

Pathological examination of the 2 excised specimens also revealed the constituents to be blood vessels that varied in size from large venules to smaller vessels surrounded by thick connective tissue sheaths. Some of the vessels contained fibrin thrombi with early endothelial cell proliferation and organization. In both cases the vessels were surrounded by lymphocytes and the endothelial cells showed the high endothelial venule change. A few angiomatoid clusters were also observed. The glial cells within the mass appeared to be of a completely benign nature.

The presence of basement membrane deposit at the retinal periphery in patient 1 but not in

Figure 7. A, Two levels through the excised mass to show attached choroid and organizing hemorrhage (hematoxylin-eosin, original magnification ×10). B, The gliotic mass contains a large organizing hemorrhage (asterisk). Hyalinized vessels (arrows) are prominent. C, Cluster of capillaries (arrows) surrounded by glial cells (hematoxylin-eosin, original magnification ×140). D, The spindle cells in the mass react with an immunohistochemical marker (glial fibrillary acid protein) for glial cells (peroxidase–antiperoxidase). The connective tissue around the vessels does not react (peroxidase–antiperoxidase, original magnification ×140). E, A thick layer of basement membrane deposit (arrows) is present beneath the tumor mass. The underlying choroid is unremarkable (picro-Mallory, original magnification ×230). F, In some sectors the retinal pigment epithelium had proliferated and undergone metaplasia to form a fibrous layer (arrows). This change was associated with an angiomatoid cluster of capillaries (hematoxylin-eosin, original magnification ×350).

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patient 2 is a frequently recognized histological abnormality and is presumably irrelevant to the retinal changes. It may be implicated in peripheral subretinal neovascularization that has been described in a wide spectrum of ocular disease.\(^7\)

The histological features of these cases have allowed a more specific interpretation of these peripheral retinal vascular lesions. We suggest that the new term—reactionary retinal glioangiosis—would seem a more appropriate descriptive term for the clinical entity previously classified as primary vasoproliferative retinal tumor.\(^2\) This supports the

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**Figure 8.** A. The excised specimen was an ovoid mass with an adjacent flattened area; the latter contains yellow flecks (arrows). Blood vessels can be identified on the surface of the tumor (original magnification \(\times 10\)). B. At the anterior periphery of the tumor, a layer of metaplastic retinal pigment epithelium (RPE) cells lined the outer surface, while the adjacent strip of inner tumor tissue contained numerous spaces of varying size, some of which contained fibrin and finely granular material (arrow) (hematoxylin-eosin, original magnification \(\times 15\)). C. Proliferation of endothelial cells (arrows) and thrombosis within tumor blood vessels (hematoxylin-eosin, original magnification \(\times 140\)). D. The nature of the spindle cells was identified with glial fibrillary acid protein (vector vacuum infiltration processor). Note lack of staining in hyalinized blood vessels (vessels can be identified on the surface of the tumor original magnification \(\times 350\)). E. Fibrin is identified within the stroma (asterisk) and thrombosed vessels (arrow) of the tumor. Note the hyalinized vessel wall (Martius scarlet blue, original magnification \(\times 140\)). F. A mass of RPE cells within choroid contained columnar cells at the periphery (arrow) and more loosely arranged cuboidal cells in the center (Masson trichrome, original magnification \(\times 230\)).
suggestion by Khawly et al\textsuperscript{16} that the significant proliferative activity is astrocytic and that presumably the vascular component is secondary to the release of vasoformative factors by the glial cells.

CONCLUSION

Both of our patients underwent surgery as management for suspected malignant melanomas. It was clear during the surgical procedure that the diagnosis was in question because of the absence of choroidal involvement. However, in cases in which the presence of a malignant melanoma cannot be excluded, local transcleral resection can avoid an unnecessary enucleation and also provides tissue to enable definitive histological diagnosis. We believe such a procedure has a place in the management of these peripheral vasoproliferative retinal tumors that form an important part of the differential diagnosis of an intraocular mass.