Bilateral Massive Retinal Gliosis Associated With Retinopathy of Prematurity

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Massive retinal gliosis (MRG) is a rare, benign intraocular condition that may develop in association with long-standing eye conditions including chronic inflammation, vascular disorders, glaucoma, trauma, or congenital abnormalities. It is thought to represent a nonneoplastic reactive tissue response to retinal injury. Here, we describe an unusual case of bilateral MRG in association with retinopathy of prematurity. To our knowledge, this may be the first report of such an occurrence. The differential diagnosis of MRG is discussed with specific emphasis on its relationship to vasoproliferative tumor of the retina and presumed acquired retinal hemangiomas. In addition, we hypothesize that MRG, vasoproliferative tumor of the retina, and presumed acquired retinal hemangiomas may represent different phenotypes along a spectrum of the same disease process.

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In 1918, von Hippel1 described 2 cases of a “benign growth of the retina.” In 1926, “massive gliosis of the retina” was used by Friedenwald2 to describe a “benign, noninvasive growth of highly differentiated glial cells,” that was based on 4 cases. In 1971, Yanoff et al3 reported 38 cases of massive gliosis of the retina. The author defined 3 criteria for massive gliosis of the retina: (1) segmental or total replacement of the retina by glial tissue; (2) abnormal blood vessels within the glial mass; and (3) obliteration of the normal retinal architecture by the proliferating glial tissue. In conclusion, Yanoff et al3 reported that all the lesions were a “non-neoplastic tissue response to retinal injury,” that may develop in association with congenital malformations, trauma, vascular disorders, and chronic inflammatory conditions resulting in atrophic phthisis bulbi. Nork et al4 determined that the cell of origin in massive retinal gliosis (MRG) was the Müller cell, and recent studies by Inayama et al5 have revealed the polyclonal nature of MRG. Only one patient with MRG was associated with retinopathy of prematurity (ROP).3 In addition, only 2 cases of bilateral MRG have been reported in the literature, 1 case with bilateral gonorrheal ophthalmia neonatorum,3 and another involving the optic nerves bilaterally and thought to be due to a congenital anomaly.6

We report an interesting case of bilateral massive retinal gliosis in association with ROP-related retinal detachment.

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History and Clinical Examination

A 39-year-old man, who was born 2.5 months prematurely, had retinopathy of prematurity with total retinal detachment that resulted in no light perception vision in his right eye. No treatment was attempted. The vision in the left eye was light perception until the age of 12, when the patient suffered a retinal detachment that was unsuccessfully treated. As a result, the outcome in the left eye was no light perception vision. No further details of his ocular history are available. The patient's eye remained comfortable until the age of 38 years, when the patient started to have bilateral recurrent epithelial defects in the setting of band keratopathy and phthisis with associated pain and headaches. Therapy with topical corticosteroids, nonsteroidal anti-inflammatory drugs, and antibiotics, in addition to bandage contact lenses, was ineffective, and the patient continued to have bilateral eye discomfort for an extended period of time. As a result of the bilateral “blind painful eye,” the patient underwent bilateral enucleation.

His last evaluation by an outside ophthalmologist just before enucleation revealed small eyes with a visual acuity of no light perception bilaterally and horizontal jerk nystagmus. On slit lamp examination, severe and moderate band keratopathy were present in the right and left eyes, respectively, preventing adequate assessment of the anterior segment and the fundus. A- and B-scan ultrasonography were performed and showed a large retinal mass extending into and filling almost the entire vitreous cavity in both eyes, with irregular internal reflectivity (Figure 1). Areas of orbital shadowing suggestive of calcification were also present.

Gross Evaluation, Histopathology, and Immunohistochemistry

The eyes were bisected, processed, and sectioned at the referring hospital. Gross evaluation indicated that the right eye had an anteroposterior diameter of 19 mm. The lens was opaque with a central tan-yellow discoloration. A thickened, firm tan-yellow vitreous mass was present. The left eye had an anteroposterior diameter of 17 mm. The vitreous cavity was occupied by a solid and inhomogeneous mass that contained milky-white and redish-brown translucent areas. No gross photographs were taken.
Figure 1. A-scan and B-scan ultrasonography of the right eye. Note that the lesion is echodense and fills almost the entire vitreous cavity. No posterior scleral excavation or extrascleral extension is present. Orbital shadowing is also noted. High and medium irregular internal reflectivity is present.

Microscopic examination of both eyes disclosed similar findings. The internal structures were disorganized with diffuse calcification and bone formation at the level of the retinal pigment epithelium and choroid. Calcification and neovascularization of the cornea was present. No retinal tissue could be identified. The retina was completely replaced by a nodular proliferation of uniform spindle and oval cells that filled the entire vitreous cavity (Figure 2, A). The cells had indistinct borders and prominent fibrillary processes and were arranged in a fascicular and whirled pattern (Figure 2, B). Mild cytologic atypia was present. The nodular proliferation contained scattered atypical blood vessels with thick and hyalinized walls (Figure 2, C). Some of these vessels were calcified. Eosinophilic droplets, suggestive of hyaline globules, were also present throughout the proliferation. No definite evidence of fibrous metaplasia of the retinal pigment epithelium was noted. No Rosenthal fibers, pigmented cells, or mitotic figures were present. The spindle and oval cells stained positively with glial fibrillary acidic protein (Figure 3) and vimentin. Only scattered inflammatory cells stained with p53 and Ki-67. These findings were consistent with the diagnosis of bilateral MRG.

Figure 2. Massive retinal gliosis by light microscopy. A. Low magnification shows a mass that fills most of the vitreous. B. The retina is completely replaced by a nodular proliferation of uniform spindle and oval cells that fill the entire vitreous cavity. The cells have prominent fibrillary processes and are arranged in a fascicular and whirled pattern. Scattered atypical blood vessels with thick and hyalinized walls are present. Note the predominance of the glial component over the vascular component. C. Higher magnification of an atypical blood vessel (hematoxylin-eosin, original magnifications ×5 [A], ×40 [B], and ×200 [C]).

Figure 3. Immunohistochemistry of massive retinal gliosis. Note intense staining of the cell proliferation with glial fibrillary acidic protein. The predominance of the glial component over the vascular component is also evident (hematoxylin-eosin, original magnification ×100).
COMMENT

Massive retinal gliosis is a rare, benign intraocular condition that may develop in association with long-standing eye conditions including chronic inflammation, vascular disorders, glaucoma, trauma, or congenital abnormalities. It is thought to represent a “non-neoplastic tissue response to retinal injury.” The differential diagnosis of such an intraocular lesion includes uveal melanoma, astrocytic hamartoma, retinal hemangioblastomas, tumors of the retinal pigment epithelium, intraocular metastasis, and vasoproliferative tumors of the retina (VPTR). The current case is differentiated from these alternative diagnoses based on the histopathologic features and immunohistochemistry of the lesions. Both eyes exhibited a glial proliferation that obliterated the normal retinal architecture and replaced the entire vitreous cavity. Additionally, atypical blood vessels were scattered throughout the tumor mass. These characteristics were used by Yanoff et al to define MRG. Finally, the positive immunohistochemistry result for GFAP and vimentin highlights the glial proliferation, while the negative staining for p53 and Ki-67 argues against a malignant proliferation or astrocytic hamartoma. However, the distinction between MRG and VPTR is more difficult, since both entities share similar histologic features consisting mainly of glial and vascular proliferations.

There has been much discussion and confusion about the nomenclature and classification of tumors consisting of glial and vascular proliferations since Shields et al described “presumed acquired retinal hemangiomas” in 1983. Later in 1995, Shields et al reported 103 cases and coined the term “vasoproliferative tumors of the ocular fundus” to refer to such lesions. Further, they classified these tumors into primary versus secondary, with primary tumors being unilateral and often located inferotemporally, without any association with previous ocular disease. Secondary lesions are usually smaller and occur secondary to various ocular disorders, including congenital and inflammatory disease, but only 1 case in that series was associated with retinopathy of prematurity. In 2000, Heimann et al suggested that many cases previously reported as localized retinal gliosis should actually be classified as VPTR because of similar histopathologic features. In the same year, Irvine et al proposed “reactionary retinal glioangiosis” instead of the term vasoproliferative tumors of the retina (VPTR) to describe such lesions. The authors felt that the term glioangiogenesis better encompasses the wide spectrum of reactive proliferations, including MRG. They suggest that in VPTR, the significant proliferative activity is astrocytic and that, presumably, the vascular component is secondary to the release of vasomotor factors by the glial cells.

On the basis of the histopathologic features of MRG reported here and in other studies, those of VPTR, and the presumed acquired retinal hemangiomas reported previously, we believe that the 3 entities belong to a spectrum of the same disease process. They all appear to be benign reactive proliferations of glial and vascular components associated with various retinal conditions. While in MRG the glial component predominates, in VPTR both components are largely represented. This may explain the exclusive features of VPTR, which are usually not seen in MRG. Presumed acquired retinal hemangiomas may fall on the extreme end of the spectrum, in which the vascular component predominates and massive exudation is typical. The various nomenclatures that have been proposed in the literature to describe MRG, VPTR, and presumed acquired retinal hemangiomas may in fact be describing different phenotypes of the same disease process. Additional studies are needed to determine whether these phenotypes are continuous or not and to understand the pathogenesis of glial-predominant versus vascular-predominant proliferation in these lesions. Because the terms massive retinal gliosis, vasoproliferative tumors of the retina, and presumed acquired retinal hemangiomas emphasize only 1 component found in these lesions, we agree with Irvine et al that the term reactionary retinal glioangiosis better encompasses the wide spectrum of these proliferations, since it underscores both their glial and vascular components. Although previous studies have reported a possible role for the retinal pigment epithelium in the pathogenesis of VPTR similar to that in proliferative vitreoretinopathy, we did not see evidence to support this in the present case. Although cytokeratin staining was not performed, no pigmented cells or cellular proliferation patterns suggestive of RPE were noted.

Like its histopathologic features, the case reported here also had clinical features that are more consistent with MRG. Massive retinal gliosis is typically characterized by a nodular proliferation that usually involves the posterior pole and classically fills the entire vitreous cavity. On the other hand, most cases of VPTR and presumed acquired retinal hemangiomas are associated with relatively small lesions, usually peripherally located, anterior to the equator and rarely grow substantially.

Our case of MRG is interesting for the following reasons. First, to our knowledge, the bilateral occurrence of such lesions is extremely rare with only 2 bilateral cases previously reported: 1 case with bilateral gonorrheal ophthalmia neonatorum, and another involving the optic nerves bilaterally and thought to be due to a congenital anomaly. Second, to our knowledge, only 1 case with unilateral MRG associated with ROP has been previously described. Although our patient had ROP-related retinal detachment, surgical repair was only attempted in one eye, eliminating surgical manipulation as the initial insult that stimulated the reactive proliferation. Third, this may be the first reported case of bilateral MRG in association with ROP-related retinal detachment. Fourth, this case underscores the importance of submitting enucleated phthisic eyes for histopathologic analysis, since they can harbor an unexpected finding or even an occult malignancy.

References