Massive Retinal Gliosis in Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1), an autosomal dominant syndrome, has major extraocular expressions of bilateral ptosis, diffuse and plexiform neurofibromas, optic nerve gliomas, and dysplasia of the sphenoid bone. With respect to the eye, the spectrum of involvement includes enlarged corneal nerves, Lisch iris nodules, dysplasia of the anterior chamber angle causing glaucoma, multiple choroidal nevi (formerly called fundus café au lait spots), diffuse uveal hamartomatous thickening (containing a mixture of melanocytes, Schwann cells, and occasional ganglion cells), enlarged nerves, uveal peripheral nerve tumors, and rare retinal astrocytic hamartomas. In this article, we describe the first association, to our knowledge, between massive retinal gliosis (MRG) and NF1.

Report of a Case | A 6-year-old boy had left upper eyelid ectropion, floppy eyelid syndrome, and neurofibromatosis (Figure 1A). Both his mother and maternal grandmother had NF1. In his first year of life he developed glaucoma, a vitreous hemorrhage of unknown cause, and epilepsy. Magnetic resonance imaging (Figure 1B) revealed buphthalmos, left cere-

Figure 1. Ocular and Periocular Neurofibromatosis Type 1

A, A 6-year-old boy had been born with a left facial deformity that eventually developed into an extensive plexiform neurofibroma. B, At age 1 year, magnetic resonance imaging disclosed an enlarged, left buphthalmic eye globe (arrowhead) from glaucoma, a thin optic nerve (N), and an anterior cranial fossa arachnoid cyst (AC). C, By age 6 years, the left globe had become phtthical and disorganized. There is an intravitreal mass (A), chorioidal thickening (B), and osseous metaplasia of the pigment epithelium (C). AC indicates stable arachnoid cyst. D, The enucleated globe with the cornea (CO) on the left displays a fibrous membrane (black arrowhead) on the surface of an atrophic iris. A solid tumor (T) has filled a contracted vitreous cavity. Osseous metaplasia of the retinal pigment epithelium (yellow arrowhead), striking choroidal thickening (CH), thickening of the sclera due to globe shrinkage, and enlarged but nonneummatous short posterior ciliary nerves (CN) are also present (hematoxylin-eosin, original magnification ×12.5).
bral hemispheric atrophy, an arachnoid cyst, leptomeningeal enhancement with calcifications consistent with Sturge-Weber syndrome, and a large left facial and orbital plexiform neurofibroma. The right eye was normal. The left eye slowly became phthisical. Repeated magnetic resonance imaging (Figure 1C) demonstrated a shrunken globe, a vitreous mass, and left optic nerve atrophy. An enucleation was performed because of ocular pain.

The enucleated left eyeball (Figure 1D) measured 21 × 16 × 17 mm and had enlarged posterior ciliary nerves. Histopathological examination revealed angle closure, a fibrous membrane on the iris surface, and a mass filling the vitreous cavity. There was osseous metaplasia of the retinal pigment epithelium and a small lens remnant had undergone complete fibrous metaplasia. The uvea displayed diffuse hamartomatous thickening (Figure 2A) and enlarged short posterior ciliary nerves (Figure 1D). The vitreous mass exhibited scattered cysts with cholesterol clefts (Figure 2B) and had destroyed the retina. The mass was composed of eosinophilic spindle cells with perivascular pigment deposition (Figure 2C). It did not involve the optic nerve. Glial fibrillary acidic protein and S-100 protein intensely immunostained the vitreous mass (Figure 2D). Neurofilament, synaptophysin, p53, and Ki-67 were all negative.

Discussion | Astrocytic retinal lesions are exceptional in NF1. Six vasoproliferative tumors of the retina in NF1 (reactive combination lesions of astrocytes and capillaries) have been described and could serve as a precursor of MRG in some instances. Massive retinal gliosis is typically a reactive, non-neoplastic, unilateral condition (bilaterality has been reported in 3 cases) that develops in adults (32 of 38 patients were adults in the largest series). The hallmark of MRG is a proliferation of fibrated eosinophilic spindle cells that replace the
vitreous cavity. Strong glial fibrillary acidic protein positivity confirms the diagnosis. Thickening of the vessel walls, perivascular pigmen, intraretinal cysts, and calcareous deposits (calciospheres) are also detectable.

Massive retinal gliosis is characteristically encountered in phthisical eyes after trauma, surgery, or inflammation and in other conditions such as retinopathy of prematurity or Coats disease. Our patient's MRG was probably a poorly modulated reparative response to an unexplained preceding hemorrhage in the eye. The smaller retinal vasoproliferative tumors are also seen in such settings, implying that they too are usually reactive. We doubt there is any intrinsic retinal property in NF1 that is conducive to MRG. Studies of MRG have preliminarily shown polyoidality, further supporting a reactive lesion. Immunostains for p53 and Ki-67 here are close to negative, whereas they are positive (>10% of cells) in astrocytic neoplasms. Retinoblastomas can be distinguished from MRG with imaging studies by virtue of the former's more prominent calcifications, from medulloepitheliomas that have ciliary region cysts, and from pediatric melanomas, which preferentially arise in the anterior segment of the eye.

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Subconjunctival Indocyanine Green Identifies Lymphatic Vessels

The lymphatic system maintains tissue fluid balance and immunity. It also plays an important role in pathologic conditions such as tumor metastasis and inflammation. The anatombists Arnold (in 1847) and Teichmann (in 1861) were the first to visualize and describe the conjunctival lymphatics. In 1948, Busacca identified a number of anastomosing lymphatics, which penetrated the orbital cavity near the extraocular muscles, using trypan blue dye. A better understanding of the lymphatic system in the eye could provide the basis for developing alternative therapeutic strategies for ocular diseases.

Newer techniques of fluorescence lymphography using indocyanine green (ICG) are increasingly being used in medical specialties such as vascular surgery and oncology. Lymphography using ICG is useful because there is no endogenous fluorescence in the near-infrared band (780-1500 nm) used for ICG detection and the examination does not cause tissue damage. Indocyanine green is approved for hepatic and ophthalmologic applications. We identified conjunctival lymphatic capillaries using lymphography with ICG.

Methods | This study was approved by the independent and external Hospital Agamenon Magalhaes Institutional Review Board. One of us (C.A.F.-N.) volunteered as the study participant and provided written informed consent. One vial containing 5 mg of ICG used for internal limiting membrane staining (Ophthosaios) was used to prepare a sterile aqueous ICG solution at 5%. Following topical anesthesia, 0.1 mL of this ICG solution was injected into the subconjunctival area using a 30-gauge needle through the conjunctiva approximately 3 mm away and inferotemporally from the limbus of the right eye.

Ocular imaging was performed using a confocal scanning laser ophthalmoscope (Spectralis HRA + OCT; Heidelberg Engineering Inc). For color photography, a retinal camera (TRC-50IX; Topcon Medical Systems) was used. Ophthalmic evaluation and ocular imaging were performed on a weekly basis until complete absorption of the ICG was verified.

Results | No systemic or local adverse effects were observed following the subconjunctival injection of ICG. The ICG completely cleared from the eye within 4 weeks. Minute lymph vessels (lymphatic capillaries) were identified and differentiated from blood vessels by multimodality diagnostic imaging. Metliculous analysis of the ICG lymphography revealed intermittently dilated lymphatic drainage channels under the conjunctival blood vessels (Figure).

Discussion | Three decades ago, Rayes et al studied the lymphatic distribution in the bulbar conjunctiva of 60 patients by injecting 1% trypan blue dye in different quadrants of the bulbar conjunctiva. The scheme of the lymphatic distribution in normal bulbar conjunctiva was presented and histopathologic studies confirmed the presence of lymphatic tissue. During phacotrabeculectomy surgery, Singh observed several vessels through which the dye passed after subconjunctival injection of trypan blue dye. The conclusion was that there