Retinal Reactive Astrocytic Tumor: Gene Expression Profiling

Retinal vasoproliferative tumor is a benign tumor with glial cell and vascular components. The clinical picture was well characterized by Shields and colleagues. Histopathologically, the low-grade tumor is composed of glial fibrillary acidic protein–positive spindle cells and vascular channels. A recent study demonstrated that the main component of the lesion was reactive astrocytes and suggested renaming the lesion retinal reactive astrocytic tumor. The authors questioned whether Müller cells, the major retinal glia, were involved in the reactive lesions. In this study, we examined the pathologic features and gene expression profile of an excised vasoproliferative tumor and confirmed the expression of 2 important overexpressed and underexpressed genes.

Report of a Case | A 28-year-old man presented with blurred vision in his right eye. Ocular and systemic histories were noncontributory. On examination, visual acuity was 20/40 OD and 20/20 OS. Anterior segment examination findings were unremarkable in both eyes. The inferior periphery of the right fundus exhibited a yellow elevated retinal lesion surrounded by a small cuff of subretinal fluid and subretinal exudates, confirmed by ultrasonography (Figure 1A). The patient initially refused treatment and returned 18 months later with visual acuity of hand motions OD. The clinical features of the lesion are demonstrated in Figure 1B. The patient underwent pars plana vitrectomy, membrane peeling, tumor resection, silicone oil tamponade, and scleral buckle. Postoperatively, visual acuity remained hand motions OD and the retina was attached under silicone oil.

Pathologic examination showed features that are demonstrated in Figure 2. Gene profiling of the tumor using normal retina as a control showed that most upregulated genes were expressed in astrocytes or reactive astrocytes or were related to inflammation and extracellular matrix function (eAppendix and eTable in Supplement). One angiogenic gene (phosphatidylinositol glycan anchor biosynthesis, class F [PIGF]) showed significant upregulation. Glial fibrillary acidic protein, which showed prominent tissue localization, was significantly upregulated but not among the top 50 upregulated genes when compared with normal retina. Gremlin and vimentin expressed by both astrocytes and Müller cells were significantly upregulated. The major pathways related to the upregulated genes included bone morphogenetic protein signaling, extracellular matrix, and inflammation. Some genes constitutively expressed in astrocytes and Müller cells were also significantly downregulated. The retinaldehyde binding protein 1 gene (RLBP1), which is specifically expressed in Müller cells, was significantly downregulated. The absence of RLBP1 expression in the tumor was confirmed by immunohistochemistry (eAppendix in Supplement and Figure 2D).

This study was approved by the institutional review board at King Khaled Eye Specialist Hospital. The patient provided oral informed consent.

Discussion | The clinical findings and course of this patient were typical of what was previously described in patients with vasoproliferative tumor. Also, many of the histological features observed were typical of those previously described. This included intertwining aggregates, glial fibrillary acidic protein–positive spindle cells, prominent telangiectatic vasculature, an overall low Ki-67 index, and
proliferating retinal pigment epithelium at the base. One interesting observation not previously described in such lesions was the presence of hemosiderin-laden macrophages in the region where aggregates of Ki-67-positive glial cells were noted. We suggest that glial cell proliferation as indicated by Ki-67 may be exacerbated in areas of extravasated blood from the abnormal vasculature (Figure 2B).

Gene profiling revealed that most significantly upregulated genes were expressed in both astrocytes and reactive astrocytes. Other genes were those related to inflammation and extracellular matrix; these pathways are upregulated in reactive astrocytes. Vascular- or angiogenesis-related genes were not prominent among the significantly upregulated genes. RLBP1, which is specifically expressed by Müller cells, was significantly downregulated in the lesion. Based on these findings, we conclude that this gliovascular lesion is predominantly astrocytic and reactive in nature. We therefore agree with Poole Perry and colleagues4 that retinal reactive astrocytic tumor might be an appropriate histologic nomenclature for this lesion, although clinically it has a prominently visible vascular component.

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Subretinal Drusenoid Deposits Associated With Complement-Mediated IgA Nephropathy

Complement-mediated IgA nephropathy is the most common cause of chronic glomerulonephritis worldwide. The pathogenesis of renal damage is related to complement activation secondary to IgA immune complex deposition in the glomerulus. To our knowledge, this is the first report of IgA nephropathy associated with bilateral subretinal drusenoid deposits (SDDs). A hypothesis for the role of complement is proposed.

Report of a Case | A 42-year-old asymptomatic Asian woman was referred for fundus abnormality noted on routine examination. Family history was noncontributory. Medical history was significant for proteinuria and stage III kidney disease secondary to IgA nephropathy diagnosed 2 years previously. Renal biopsy demonstrated mesangial IgA deposition, expansion of the mesangial matrix, and positive direct immunofluorescence for complement C3 and C1q. Oral prednisone therapy was unsuccessful, and long-term treatment with mycophenolate mofetil was initiated.

Visual acuity was 20/20 OU with mild myopic correction. There were well-defined clusters of small yellow deposits in the macula with relative sparing of the central fovea (Figure 1). Spectral-domain optical coherence tomography (Cirrus; Carl Zeiss Meditec) revealed perifoveal hyperreflective convex deposits internal to the retinal pigment epithelium (RPE)-Bruch membrane band corresponding to the yellow deposits (Figure 2) and secondary elevation of the ellipsoid band with reduced reflectivity. There was poorly delineated granular reflectivity between the ellipsoid and interdigitation bands adjacent to the deposit.

Discussion | Complement-mediated IgA nephropathy presents in young adulthood with macroscopic hematuria, while older adults develop proteinuria, microscopic hematuria, and/or hypertension. Renal biopsy is diagnostic, demonstrating IgA deposits in the glomerular mesangium with complement C3 deposition. The pathogenesis of IgA nephropathy involves an error in IgA1 glycosylation resulting in IgA1 secretion into the systemic circulation. The IgA1 forms complex deposits attached to extracellular matrix and mesangial cells within the glomerulus. This induces mesangial cells to release proinflammatory mediators and activate the complement system via lectin and alternative pathways.1

The perifoveal deposits in our case are located above the RPE on spectral-domain optical coherence tomography and are consistent with SDDs. These differ from typical drusen in age-related maculopathy, which are focal elevations located between the basal lamina of the RPE and the inner collagenous layer of the Bruch membrane. The SDDs are the histopathologic correlate of reticular pseudodrusen.2 They are located perifoveally where rod density is highest and have been demonstrated in age-related macular degeneration, adult vitellin..

Figure 1. Fundus Photographs

Color fundus photographs of the right (A) and left (B) eyes show small, clustered, well-defined macular deposits with relative sparing of the central fovea.