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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 vitelli-

Figure 1. Fundus Photographs

A B

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.
form macular degeneration, pseudoxanthoma elasticum, and fundus albipunctatus. Composition of the SDDs is similar to that of soft drusen containing unesterified cholesterol, apolipoprotein E, and complement factor H (CFH).

The renal glomerulus basement membrane and RPE-Bruch membrane complex are similar physiologically and exposed to immune complexes in the systemic circulation. The systemic circulation plays an important role in binding complement to drusen components. In cell culture, RPE cells have low complement immunoreactivity with drusen components. However, when RPE cells are exposed to human serum, a striking activation of terminal C5b-9 complex bound to drusen components is observed. Circulating serum IgA1 complexes should respect the blood-retinal barrier and would be unlikely to deposit in the subretinal space where SDDs are located. One hypothesis is that IgA1 complexes deposit on the basal surface of the RPE cell, causing activation similarly as in the renal mesangium. Activated RPE cells can bidirectionally secrete lipoproteins, and SDD formation may develop after apical secretion. This is supported by studies demonstrating that CFH plays a role in the subretinal space. The CFH regulates the alternative pathway by binding to C3b and acting as a cofactor for complement factor I. In cultured polarized RPE cells, CFH localizes to the cell's apical surface, and in CFH knockout mice, photoreceptor damage is observed with minimal sub-RPE change. Complement cross-reactivity may provide a link between SDDs and IgA nephropathy.

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Loop-Mediated Isothermal Amplification for Rapid Diagnosis of Tubercular Uveitis

Polymerase chain reaction (PCR) to detect *Mycobacterium tuberculosis* in tubercular uveitis is limited by low sensitivity, expensive equipment, sophisticated laboratory facilities, and expertise. We evaluated loop-mediated isothermal amplification (LAMP) assay targeting the IS6110 region of *M. tuberculosis* in intraocular samples from patients with tubercular uveitis.

Methods | The Institute Ethics Committee of the Post Graduate Institute of Medical Education and Research approved this study, and written informed consent was obtained from the patients. A total of 29 vitreous fluid samples from eyes undergoing pars plana vitrectomy and 1 iris biopsy sample were subjected to LAMP assay under the following groups: (1) group 1 (10 patients) with tubercular uveitis confirmed by positive multitargeted PCR for *M. tuberculosis* from intraocular samples; (2) group 2 (10 patients) with intraocular inflammation due to nontubercular etiology (negative controls); and (3) group 3 (10 patients) with vitreoretinal disorders without any intraocular inflammation (normal controls).

After DNA extraction, LAMP was performed using 6 primers specific for the IS6110 region of *M. tuberculosis*5: (1) F3, 5′-AGACCTCACCTATGTGTCGA-3′; (2) B3, 5′-TCGCTGAACCGGATCGA-3′; (3) FIP, 5′-ATGGAGGTGGCCATCGTGGAAGCCTACGTGGCCTTTGTCAC-3′; (4) BIP, 5′-AAGCCATCTGGACCCGCCAACCCCCATCGTATGGTGAG-3′; (5) FLP, 5′-AGGATCCTGCGAGCGTAG-3′; and (6) BLP, 5′-AAGAAGGGCTACTCGACCTG-3′.

The entire reaction could be conducted under isothermal conditions, requiring only a water bath or heating block at 60°C to 65°C. The needs for electrophoresis, specialized equipment (thermocycler), and technical expertise were eliminated. Amplification products were detected by the following: (1) agarose gel-based analysis showing a typical ladder pattern in positive reaction (Figure 1); or (2) naked eye using 0.1% SYBR Green 1 (Life Technologies) and observing the color of the solution under UV light, turning green in the presence of a LAMP amplicon but remaining orange with no amplification (Figure 2).

Results | The mean (SD) ages were 42.5 (9.8) years (range, 30-50 years) in group 1 (7 male, 3 female), 34.4 (20.2) years (range, 3-60 years) in group 2 (5 male, 5 female), and 40.6 (17.1) years (range, 8-63 years) in group 3 (7 male, 3 female). Seven samples in group 1 (70%) tested positive by LAMP. All samples in groups 2 and 3 were negative by both LAMP and multitargeted PCR. The sensitivity, specificity, positive predictive value, and negative predictive value of LAMP assay were 70%, 100%, 100%, and 62.5%, respectively.