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Manifestations of Complement-Mediated and Immune Complex-Mediated Membranoproliferative Glomerulonephritis

A Comparative Consecutive Series

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Purpose: Membranoproliferative glomerulonephritis (MPGN) recently was reclassified to reflect the underlying cause as a complement-mediated and immune complex-mediated disease. This classification is based on renal biopsy immunofluorescence examination, making the former electron-microscopy classification obsolete. In this report, we describe related eye findings in patients with MPGN based on the new classification.

Design: Retrospective case series.

Participants: All Mayo Clinic Rochester patients with pathology-confirmed complement- and immune complex-mediated MPGN who had available ophthalmology records from 1997 through 2014 were included in this study.

Methods: The medical and pathologic records of patients with MPGN and eye examination results were reviewed from years 1997 through 2014.

Main Outcome Measures: The number of patients and the number of eyes with MPGN-related pathologic features were examined. Visual acuity also was considered.

Results: There were 23 patients with complement-mediated MPGN and available eye examination results. Of these, 9 patients (39%) and 17 eyes (37%) had retinal pathologic features that likely were related to the same underlying pathophysiologic process as their renal disease. Five patients (22%) and 6 eyes (13%) had significant vision loss. There were 23 patients with immune complex-mediated MPGN and available eye examination results. Only 2 (9%) of these patients (4 eyes) had retinal pathologic features that potentially could be related to the same underlying pathophysiologic process as their renal disease, and neither had vision loss.

Conclusions: Retinal abnormalities are more prominent among patients with complement-mediated MPGN when compared with patients with immune complex-mediated MPGN. It is critical for ophthalmologists to recognize the updated MPGN classification system, and all patients with complement-mediated MPGN require screening eye examinations. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology.*

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury resulting from predominantly subendothelial and mesangial deposition of immune complexes, complement factors, or both. As such, MPGN is not a disease diagnosis; rather, it is a descriptive term for a certain type of glomerular damage.

Membranoproliferative glomerulonephritis traditionally has been classified into types I, II, and III based on electron microscopy findings.[1,2] Type I is characterized by discrete immune deposits in the mesangium and subendothelial space. Type II (also called dense-deposit disease [DDD]) is characterized by continuous, dense ribbon-like deposits along the basement membranes of the glomeruli, tubules, and Bowman's capsule. Type III is characterized by subepithelial deposits in addition to deposits in the mesangium and subendothelial space. However, considering that some cases of glomerulonephritis are immune complex mediated, whereas others are complement mediated, it became clear that the electron microscopy-based classification could not differentiate between the 2 types, and thus was unhelpful in directing proper clinical evaluation and disease-specific treatment. Thus, a new MPGN classification based on the etiologic process has been proposed.[3,4] Ophthalmologists had been concerned primarily with type II MPGN, or DDD, because of its well-known association with drusen-like deposits as well as reports of associated choroidal neovascularization and idiopathic central serous chorioretinopathy.[5–18] In fact, deposits appeared similar in both Bruch's membrane and the glomerular basement membrane on electron microscopy.[19–21] However, reports started to surface of drusen associated with glomerular lesions other than DDD (called C3 glomerulonephritis [C3GN]).[22,23] Moreover, clinicians began to recognize an association between the drusen found in some patients with

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DDD and mutations in complement factor H (*CFH*).[21,24,25] It is now becoming clear that the molecular cause of the disease process needs to be examined more closely when considering which patients are at increased risk for the development of ocular pathologic features and vision loss.

Under the new classification, MPGN is divided into 2 types: immune complex-mediated MPGN and complement-mediated MPGN (C3 glomerulopathy).[3,4] The former DDD and the newly recognized C3GN both fall under the classification of complement-mediated MPGN because these disease processes are a result of glomerular deposition of complement factors and degradation products formed as a result of overactivation of the alternative complement pathway.[26–29] However, neither MPGN type I nor MPGN type III can be classified distinctly as complement mediated or immune complex mediated. Thus, it becomes important to re-examine the association of MPGN with ocular pathologic features in the setting of this new classification. Herein, we characterize the eye findings of patients with both complement-mediated and immune complex-mediated MPGN and emphasize the importance of the new MPGN classification system to the ophthalmologist.

Methods

Mayo Clinic electronic records were searched using the Data Discovery and Query Builder (IBM, Rochester, MN) for all patients with MPGN between 1997 and 2014. The search was performed using 3 unique International Classification of Diseases, Ninth Edition, codes (581.2, 582.2, and 583.2) and was limited to patients with available pathologic records. To ensure inclusion of all patients with MPGN, patients with the word *membranoproliferative* included in the pathology report were included in the initial search even in the absence of 1 of the 3 selected International Classification of Diseases, Ninth Edition, codes. The 662 results were narrowed by manual review to 73 patients who had undergone dilated eye examinations. Manual review of all pathology reports for the remaining 73 patients resulted in the elimination of 27 patients for whom pathology reports did not support a diagnosis of MPGN. Of the remaining 46 patients, 23 had pathology-proven complement-mediated MPGN and 23 had pathology-proven immune complex-mediated MPGN, spanning a 15-year period from 2000 through 2014. These 46 records were examined in detail. When fundus imaging, including color photographs, optical coherence tomography images, and fluorescein angiography images were available, the images were reviewed with one of the authors (J.S.P.). Microsoft Excel (Microsoft, Redmond, WA) was used to calculate averages, standard deviations, and *t* test values. This study complied with Health Insurance Portability and Accountability Act, and the Mayo Clinic Institutional Review Board approved this study.

Results

Complement-Mediated Membranoproliferative Glomerulonephritis

The medical records of 23 patients, 9 women and 14 men, with complement-mediated MPGN were examined in detail. At the time of first eye examination available in the Mayo system, the average age of the patients was 41±21 years. Retinal pathologic features, if present at any time, were evident on the initial examination for all patients. Six of the patients were deceased at the time of record review. Patients were diagnosed with pathology-confirmed complement-mediated MPGN at an average age of 40±20 years, and patients had an average of 8±5 years of follow-up available in the electronic records after renal diagnosis. Of these 23 patients, 10 (43%) had no ocular pathologic features, 4 (17%) had likely unrelated ocular findings (central retinal vein occlusion, nonproliferative diabetic retinopathy, pigment dispersion syndrome, multifocal choroiditis), and 9 (39%) had retinal findings likely related to complement-mediated MPGN (Fig 1). Of the 46 eyes, 17 (37%) were affected. In particular, 6 patients (26%) and 12 eyes (26%) had drusen, 1 patient (4%) and 2 eyes (4%) had nonspecific retinal pigment changes, 1 patient (4%) and 2 eyes (4%) had bone spicule pigment changes, and 1 patient (4%) and 1 eye (2%) had a retinal detachment with pigment changes (Table 1). Of the 9 patients with MPGN-related retinal findings, 5 patients (22%), 3 women and 2 men, and 6 eyes (13%) had a best-corrected distance visual acuity of 20/200 or worse on the most recently documented eye examination. Image findings are shown for the patient with poor acuity in both eyes (patient 7) in Figure 2. Of note, patient 7 had a decrease in subretinal fluid and an improvement in visual acuity from 20/400 to 20/200 in both eyes with monthly aflibercept injections. An additional patient had a field deficit corresponding to the area of drusen in both eyes despite 20/20 acuity in each eye. The remaining 3 patients corrected to 20/20, and the image findings for one of these patients (patient 3) are shown in Figure 3. The average visual acuity of all 46 eyes was 0.29±0.6 logarithm of the minimum angle of resolution (logMAR). The logarithm of the minimum angle of resolution equivalents of 2.8 and 2.9 were used for light perception only and no light perception vision, respectively. The average time from renal diagnosis to first recognition of retinal pathologic findings was 6±3 years, but this ranged from concurrent diagnoses to 9 years after renal diagnosis. The average age of development of retinal pathologic features was 30±11 years. Of the 9 patients with retinal pathologic features, 2 had MPGN type I, 1 had MPGN type II, and 1 had MPGN type III based on the previous MPGN classification; re-examination of the biopsy samples showed that these belonged to the complement-mediated MPGN group. The remaining 6 patients were not classified under the old system, but all were classified as complement-mediated MPGN. Molecular typing was available in 3 patients, all of whom had both drusen and *CFH* risk-associated alleles, and 1 of whom had *C3* risk-associated alleles as well. In those with risk-associated alleles, drusen developed at as young as 22 years of age, but the youngest patient for whom genetic testing was unavailable with first retinal pathologic features was 18 years of age.

Regarding systemic treatment for renal disease, of the 9 patients with eye findings, 4 required renal transplantation (patients 1, 2, 5, and 9), 2 were treated with the C5 inhibitor eculizumab (patients 7 and 8), 1 was stable with prednisone and mycophenolate mofetil (patient 4), and 2 were stable systemically without any immunosuppressive or immunomodulatory therapy (patients 3 and 6). Interestingly, the 2 patients who did not require immunosuppressive therapy for their renal disease maintained 20/20 visual acuity in both eyes, whereas 3 of the 4 patients requiring transplantations (patients 1, 2, and 5) experienced severe visual loss in 1 eye. The patient maintained with immunosuppressive therapy (patient 4) also had severe visual loss in 1 eye. Of the