MAYO CLINIC

ORIGINAL ARTICLE

Hematologic Characteristics of Proliferative Glomerulonephritides With Nonorganized Monoclonal Immunoglobulin Deposits

Gauri Bhutani, MBBS; Samih H. Nasr, MD; Samar M. Said, MD; Sanjeev Sethi, MD, PhD; Fernando C. Fervenza, MD, PhD; William G. Morice, MD, PhD; Paul J. Kurtin, MD; Francis K. Buadi, MD; David Dingli, MD, PhD; Angela Dispenzieri, MD; Morie A. Gertz, MD; Martha Q. Lacy, MD; Prashant Kapoor, MD; Shaji Kumar, MD; Robert A. Kyle, MD; S. Vincent Rajkumar, MD; and Nelson Leung, MD

Abstract

Objective: To study the hematologic characteristics of proliferative glomerulonephritides (GNs) from nonorganized glomerular monoclonal immunoglobulin (MIg) deposition (MIPG).

Patients and Methods: The pathology database at Mayo Clinic (Rochester, Minnesota) was used to find patients with MIPG who underwent a kidney biopsy between January 1, 2008, and December 31, 2013. Retrospective medical record review was conducted in the identified cohort (N=60).

Results: The median patient age was 56 years (interquartile range, 47-62 years) and the estimated glomerular filtration rate was 36 mL/min/1.73 m^2 (interquartile range, 22-52 mL/min/1.73 m^2). Most patients had IgG MIg deposits (90%; 54 of 60) and a membranoproliferative pattern (48%; 29 of 60). A circulating nephropathic MIg was detected by serum immunofixation ($SIFE^+$) in 20% (12 of 59) and by abnormal serum free light chain ratio ($sFLCR^+$) in 21% (12 of 56). The subsets of $SIFE^+$ and $sFLCR^+$ incompletely overlapped. The nephropathic clone was found by bone marrow testing (BM^+) in 25% (10 of 40; 6 plasma cell clones [5 IgG; 1 IgA], 3 chronic lymphocytic leukemia [all IgG], and 1 lymphoplasmacytic clone [IgM]). The clone detection rate was significantly higher in patients with $SIFE^+$ ($P<.001$) and in those with $SIFE^+$ and/or $sFLCR^+$ ($P<.001$). Patients with $SIFE^+$ and BM^+ frequently had IgG1-restricted MIg deposits on renal biopsy immunofluorescence ($P=.005$). Most BM^+ patients required flow cytometry and immunohistochemical analysis of the marrow specimen for accurate diagnosis.

Conclusion: Undetectable circulating nephropathic MIg and pathologic clones characterize most MIPG. Immunoglobulin isotype may predict detectability of MIg and clone by currently available technology. Bone marrow evaluation, including flow cytometry and immunohistochemical analysis, should be performed for $SIFE^+$ and/or $sFLCR^+$. More sensitive clone-identifying techniques in the marrow and extramedullary tissue are needed when SIFE and sFLCR test negative.

 ■ Mayo Clin Proc. 2015;90(5):587-596

Monoclonal gammopathy of renal significance (MGRS) is a recently introduced term to differentiate monoclonal gammopathy of undetermined significance (MGUS) from monoclonal gammopathies that result in kidney disease without underlying multiple myeloma or malignant B-cell lymphoproliferative disorders.[1] Kidney diseases associated with MGRS are most commonly the consequence of renal deposition of monoclonal immunoglobulin (MIg) or its components.[1,2] Owing to the variety of renal pathologic abnormalities that can result from MIg deposition, these diseases are currently categorized based on the substructure of MIg deposits. Organized deposits may be fibrillar, as in immunoglobulin light chain amyloidosis; microtubular, as in immunotactoid and cryoglobulinemic glomerulonephritides (GNs); or crystalline, as in light chain proximal tubulopathy (Fanconi syndrome). Nonorganized MIg deposits can be seen in MIg deposition disease

From the Division of Nephrology and Hypertension (G.B., F.C.F., N.L.), Department of Laboratory Medicine and Pathology (S.H.N., S.M.S., S.S., W.G.M., P.J.K.), and Division of Hematology (F.K.B., D.D., A.D., M.A.G., M.Q.L., P.K., S.K., R.A.K., S.V.R., N.L.), Mayo Clinic, Rochester, MN.

(MIDD) and proliferative GN (PGN) with monoclonal IgG deposition (PGNMID).[1]

The clinical and pathologic characteristics of PGNMID are well described, and its rapid recurrence in the allograft after kidney transplant is recognized.[3-5] Rare cases of PGNs with nonorganized monoclonal IgA or IgM (non-IgG PGNs) have also been reported.[6,7] There is, however, no clinical trial–based treatment strategy for either PGNMID or non-IgG PGN.[3,5] In most MGRS-related kidney diseases, the nonmalignant MGRS does not immediately affect patient survival but causes progressive renal disease that often results in end-stage renal disease.[1] Effective protection of native renal function and successful kidney transplantation requires elimination of the nephropathic MIg by treatment tailored to the identity of the nephropathic clone.[8] To formulate future treatment strategies, we undertook this study to investigate and better understand the hematologic characteristics of PGNMID and non-IgG PGN. For this study, we use the term *MIg (nonorganized) proliferative glomerulonephritis* (MIPG) to refer to both PGNMID and non-IgG PGN.

PATIENTS AND METHODS

The Mayo Clinic (Rochester, Minnesota) renal pathology database between January 1, 2008, and December 31, 2013, was queried for the following terms: (*mesangioproliferative* or *membranoproliferative* or *diffuse proliferative*) and *monoclonal*. The patient inclusion criteria were (1) native or allograft biopsy demonstrating a PGN, (2) presence of MIg deposits on immunofluorescence, and (3) nonorganized deposits on electron microscopy. We excluded patients with organized deposits or MIDD and inadequate evidence of MIg deposits. We also excluded patients in whom MIPG was diagnosed incidentally on protocol-based post–kidney transplant biopsies who were asymptomatic.

The first biopsy that fulfilled the inclusion criteria became the baseline data collection time point. Demographic and clinical information was collected from the electronic medical record and outside history when available. In particular, data on renal function, MIg testing, and clone detection were noted. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease (CKD) epidemiology collaboration equation.[9] The amount of proteinuria was confirmed by 24-hour urine testing if the random sample estimate was greater than 100 mg/d. The MIg testing included serum and urine protein electrophoresis and immunofixation. The standard serum free light chain ratio (sFLCR) range (0.26-1.65) was used to denote monoclonality.[10] Clone detection studies included bone marrow (BM) testing, peripheral blood flow cytometry, bone survey, bone scan, and positron emission tomography–computed tomography, all performed per physician preference. Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) gives details on the various techniques used to evaluate the BM biopsy.

Statistical analysis was performed using JMP Pro 10.0 (SAS Institute Inc). Continuous variables are reported as median (interquartile range [IQR]). Categorical variables are reported as number (percentage). Categorical variables were compared using the Fisher exact test. The Wilcoxon rank sum test was used to compare nonparametric continuous variables between groups. Statistical significance is assumed at $P<.05$. The Institutional Review Board of the Mayo Clinic Foundation approved this study as minimal risk and exempted participant consent and Health Insurance Portability and Accountability Act authorization.

RESULTS

Demographic and Clinical Characteristics

One hundred fifty-seven patients were identified from the database. Of these, 60 patients fulfilled the inclusion criteria and form the study cohort. Fifty-four patients (90%) had IgG-based MIg deposits consistent with PGNMID. Six patients (10%) had non-IgG deposits (4 IgMλ, 1 IgMκ, and 1 IgAκ). Overall, the median patient age was 56 years (IQR, 47-62 years). Twenty-eight patients (47%) were women and 32 (53%) were men. In 3 of 60 patients, MIPG was first diagnosed in a renal allograft; these patients had undergone transplantation for an unknown native kidney disease.

In the present cohort, the median eGFR at presentation was 36 mL/min/1.73 m^2 (IQR, 22-52 mL/min/1.73 m^2; n=60), and the median 24-hour urine proteinuria was 3.6 g/d (IQR, 1.9-8.1 g/d; n=49). The serum albumin level was less than 3 g/dL in 33% of patients (14 of 43). Table 1 details the demographic

Mayo Clin Proc. ■ May 2015;90(5):587-596 ■ http://dx.doi.org/10.1016/j.mayocp.2015.01.024
www.mayoclinicproceedings.org