Patterns of Noncryoglobulinemic Glomerulonephritis with Monoclonal Ig Deposits: Correlation with IgG Subclass and Response to Rituximab

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Summary

Background and objectives Several different entities have recently been described among glomerular diseases associated with monoclonal IgG deposits. The aim of this study was to describe the distribution of the different pathologic subtypes of IgG-associated glomerulopathy and to evaluate the IgG isotype involved in these diseases.

Design, setting, participants, & measurements This was a retrospective study including all patients with glomerular deposits of monoclonal IgG referred to three nephrology departments between 1980 and 2008.

Results Twenty-six patients were included. Nephrotic syndrome was almost constantly associated with a renal dysfunction in 14 of 26 patients. The presence of M-spike was detected in only 30% of the patients, and an overt hematologic malignancy (myeloma, lymphoma) was identified in 9 of 26 patients. Patients were almost equally divided into two distinct histologic patterns: membranous nephropathy (MN) or membranoproliferative glomerulonephritis (MPGN). IgG3 deposits were identified in 80% of patients with MPGN, whereas IgG1 deposits were present in 64% of patients with MN. Ultrastructural study showed that immune deposits were nonorganized in most patients. Seven patients were treated with rituximab with excellent results: five of seven had a complete remission of the nephrotic syndrome and two of seven had a partial response. After a mean 24-month follow-up, only one patient experienced relapse of the nephropathy.

Conclusions GN with monoclonal Ig deposits can be associated with MPGN or MN, which are correlated with IgG3 and IgG1 isotypes, respectively. Rituximab appears to have a very favorable benefit-to-risk ratio for patients with no overt hematologic malignancy.

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Introduction

Monoclonal immunoglobulins (Ig) can affect the kidney in several ways involving the deposition of an entire Ig or of its components, including free light chains or heavy chains (1,2). The clinical spectrum of hematologic diseases associated with kidney deposition or precipitation of monoclonal Ig includes multiple myeloma (MM), Waldenström macroglobulinemia, chronic lymphocytic leukemia (CLL), and B cell lymphomas; however, in most patients, there is no identified hematologic malignancy. Glomerular diseases in patients with monoclonal Ig can be classified in two categories by electron microscopy (EM). The first category includes diseases with fibril formation, mainly amyloidosis, and diseases with microtubule formation, including cryoglobulinemic and immunotactoid GN (3–5). The second category is characterized by nonorganized electron-dense granular deposits. They are localized along basement membranes in most tissues, especially in the kidney, and define a disease now termed "monoclonal Ig deposition disease" (6). In addition, Nasr *et al.* have recently described a novel form of glomerular disease, termed "proliferative glomerulonephritis with monoclonal IgG deposits," in which monoclonal Ig deposits are associated with glomerular proliferative lesions, mimicking different patterns of immune-complex GN, such as membranoproliferative or endocapillary proliferative GN (7,8).

We herein describe the results of a retrospective study including 26 patients diagnosed with a glomerulopathy and monoclonal IgG deposits. The aim of this study was to describe the distribution of the different pathologic subtypes of IgG-associated glomerular disease, to search for a correlation between the glomerular pattern and the IgG isotype, and to evaluate the response of these rare diseases to novel treatments of hematologic malignancies, such as rituximab.

Materials and Methods

All patients with glomerular deposits of monoclonal IgG who were referred to our nephrology departments (Hôpital Tenon; Hôpital Necker, Paris; Hôpital Foch, Suresnes) between 1980 and 2008 were included in this retrospective study. Inclusion criteria (based on light and immunofluorescence microscopy studies of renal biopsy) were presence of GN associated with glomerular monotypic IgG deposits (positive staining for a single light-chain isotype, λ or κ) without associated IgA or IgM deposits. Patients with AL amyloidosis, light- or heavy-chain deposition disease, or cryoglobulinemic GN were excluded from this study. Fibrillary GN, resulting from polyclonal IgG4 deposition, was excluded when both light chains were detected in glomerular deposits.

Patients' medical records were reviewed for demographic information, clinical and laboratory findings, renal pathology findings, treatment, and outcome. All kidney biopsy samples were processed for light and immunofluorescence microscopy according to standard techniques. In 21 patients, subclasses of glomerular IgG deposits were determined using monoclonal anti-IgG1, IgG2, IgG3, and IgG4 antibodies (provided by Margaret Goodall, Recognition Sciences Ltd., Birmingham, United Kingdom). An EM study was only available in 14 patients because this diagnostic procedure is not done routinely. The degree of interstitial fibrosis and tubular atrophy was stratified into absent or mild (0% to 25% of cortical surface area), moderate (26% to 50%), and severe (>50%).

Nephrotic syndrome was defined as 24-hour urine protein >3 g/d with hypoalbuminemia (serum albumin <30 g/L). Renal dysfunction was defined as an estimated GFR (eGFR) <60 ml/min per 1.73 m^2 with the Modification of the Diet in Renal Disease formula. Microscopic hematuria was defined as the presence of >10,000 erythrocytes/mm^3 on microscopic examination of urinary sediment. Hypertension was diagnosed when systolic BP was >140 mmHg and/or diastolic pressure was >90 mmHg.

The following definitions were used for analysis of renal outcomes: complete remission (CR) was defined by proteinuria <0.5 g/d, stable or improved renal function, and serum albumin >30g/L. Partial remission (PR) was defined by proteinuria between 0.5 and 3 g/d, stable or improved renal function, and serum albumin >30 g/L. Nonremission (NR) was defined as >20% renal function deterioration and/or persistence of nephrotic syndrome. Relapse was defined as reappearance of nephrotic syndrome after CR or PR.

For statistical analysis, quantitative data were reported as means ± SDs and compared using the *t* test or variance analysis. Qualitative variables were reported as absolute numbers and percentages and were compared with the χ^2 test. Statistical significance was assumed at $P < 0.05$.

Results

Renal Presentation

Twenty-six patients (16 women and 10 men) were retrospectively included in this study. The main demographic, clinical, and biologic characteristics are detailed in Table 1.

At presentation, all patients had glomerular proteinuria >1 g/24 h and most (85%) patients presented with nephrotic syndrome. Mean serum creatinine level at presen-

Table 1. Demographic, clinical, and biological characteristics at presentation

Characteristic	Value
Female/male, *n* (%)	16/10 (61/39)
Age, years (mean ± SD) (range)	52 ± 16 (29 to 77)
≥40 years, *n* (%)	20 (77)
<40 years, *n* (%)	6 (23)
Ethnicity, *n* (%)	
Caucasian	22 (85)
other	4 (15)
Proteinuria, g/24 h (mean ± SD) [range]	5.3 ± 4.6 [1.4 to 10]
Serum albumin, g/L (mean ± SD) [range]	26 ± 7 [13 to 46]
Total serum protein, g/L (mean ± SD) [range]	55.1 ± 6.1 [46 to 65]
Nephrotic syndrome, *n* (%)	22 (85)
Hematuria, *n* (%)	21 of 24 (87.5)
Serum creatinine, μmol/L (mean ± SD) [range]	211 ± 190 [45 to 814]
eGFR, ml/min per 1.73 m^2 (mean ± SD) [range]	49.3 ± 34.6 [10 to 130]
Renal dysfunction, *n* (%)	14 (54)
Hypertension, *n* (%)	16 of 24 (66.7)
Dysproteinemia, *n* (%)	8 (30.7)
serum paraprotein only	6 (23)
serum and urine paraprotein	2 (7.7)
Hematological malignancy, *n* (%)	9 of 26 (34.6)
Low C3, *n* (%)	1 of 22 (4.5)
Low C4, *n* (%)	3 of 22 (13.6)
Low C3 and C4, *n* (%)	4 of 22 (18.1)
Adenopathy, *n* (%)	2 (7.7)
Hepatosplenomegaly, *n* (%)	1 (3.8)

eGFR, estimated GFR.

tation was 211 μmol/L (eGFR 49.3 ± 34.6 ml/min per 1.73 m^2), and 14 of 26 (54%) patients initially had significant renal dysfunction, including three patients who needed temporary hemodialysis.

Hematology and Immunology Findings

In eight patients (31%), a circulating monoclonal IgG was detected by standard methods (serum and urine protein electrophoresis with immunofixation). Two of these patients had serum and urine monoclonal IgG detected. In all of these patients, the serum monoclonal IgG had the same light-chain and heavy-chain isotype as the monoclonal compound identified in the glomerular deposits on the renal biopsy. Most patients in this study were investigated before Freelite dosage of circulating light chain was largely available.

Bone marrow examination and blood lymphocyte phenotype were performed in 22 of 26 patients and an hematologic malignancy was identified in 9 of them: 2 had MM, 4 had CLL, and 3 had non-Hodgkin lymphoma (NHL). Five of the patients with malignancy had detectable serum monoclonal IgG. The hematologic disease was revealed by the nephropathy in four of nine patients, whereas four patients had a long-standing history of hemopathy when GN was detected (mean delay was 32 months [3 to 89]). One patient, who was initially diagnosed with monoclonal gammopathy of undetermined significance, converted to overt MM 81 months after the onset of renal disease. A positron emission tomography scan was performed in three patients with no proven hematologic malignancy and found no tumoral mass.

Hypocomplementemia was observed in 8 of 22 patients (36%) with available data and showed either isolated C4 or combined C3/C4 consumption. Low serum complement concentration was equally observed among patients with either MPGN or MN histologic pattern and independently of the monoclonal IgG isotype. Serum cryoglobulin, hepatitis C, hepatitis B, and HIV serological test results were negative in all patients.

Pathologic Findings

Light Microscopy Examination of Renal Biopsy. The most common pathologic pattern was membranous nephropathy (MN), which was observed in 14 of 26 patients (Figure 1, A and B). In five of these patients, the glomerular lesions were atypical with mesangial hypertrophy and increased mesangial cellularity. Membranoproliferative glomerulonephritis (MPGN) was the second most frequently observed type of glomerular disease. MPGN was present in 12 of 26 patients, characterized by diffuse double-contoured glomerular capillary walls and mesangial cell interposition (Figure 1, C and D). Overall, extracapillary proliferation with crescents was observed in 13 patients (4 of 14 in MN, 9 of 12 in MPGN) whereas glomerular necrotic lesions were present in only six biopsies. Interstitial inflammation with infiltration by neutrophils and nonmalignant lymphocytes was noted in 17 patients (65%). Interstitial fibrosis with tubular atrophy ranged from absent or mild (57%) to moderate (27%) and severe (16%). Vascular lesions were frequent, mainly arteriolar hyalinosis (15 of 26) and arteriosclerosis (19 of 26).

There was no major difference between MN and MPGN patients when comparing clinical and laboratory data. The only significant difference was lower eGFR at presentation in patients with MPGN (35.7 ± 21.3 *versus* 66.8 ± 35.4 ml/min per 1.73 m^2, $P = 0.013$). Light microscopy findings were not significantly different between the two groups when comparing presence and degree of glomerulosclerosis, extent of interstitial inflammation, interstitial fibrosis, and tubular atrophy.

Immunofluorescence Study. In all patients, the IgG deposits were granular and localized only in glomeruli. The deposits were found along the subepithelial side of the basement membrane in MN (Figure 1E) and in the glomerular capillary walls and mesangium in MPGN (Figure 1F). Interestingly, five MPGN patients had associated minor membranous deposits.

Light-chain isotype restriction was found in all patients with positivity for κ light chain in 80% of patients. The subclasses of IgG deposits were determined for 21 patients: deposits stained for γ1 in 8 patients (6 IgG1κ and 2 IgG1λ), γ2 in 2 patients (IgG2κ), γ3 in 10 patients (9 IgG3κ and 1 IgG3λ), and γ4 in 1 patient (IgG4κ).

IgG subclass distribution was different according to the observed glomerular pattern: IgG3 deposits were identified in 80% of patients in MPGN (seven of eight IgG3κ, one of eight IgG3λ), whereas only 18% of MN had IgG3 deposits ($P = 0.0021$). On the other hand, IgG1 deposits were present in 64% of MN (four of seven IgG1κ, three of seven IgG1λ), whereas only 10% of MPGN had IgG1 deposits ($P = 0.014$).

EM Study. EM examination of renal biopsies was available for 14 of 26 patients. In most of the examined patients (11 of 14), ultrastructural study showed that immune deposits were not organized. EM demonstrated large, granular deposits that were subepithelial in eight patients (with associated mesangial deposits in two of them; Figure 1G) and subendothelial in three patients. In all patients, important podocytic lesions were observed, such as segmental effacement of foot processes and vacuolization of podocyte cytoplasm. Three patients had immunotactoid GN, with organized subepithelial deposits of microtubular substructure (Figure 1H). Diameter of the microtubular structures was 25 to 40 nm.

Outcome

Clinical outcome (Table 2) was available for 25 patients (96%) and the mean duration of follow-up was 67.6 months (range 2 to 216 months). One of the patients died of CLL shortly after presentation.

In patients with hematologic disorders (9 of 26), different chemotherapy schemes were used according to the underlying disease, combining steroids, alkylating agents (chlorambucil, cyclophosphamide, or melphalan), fludarabine, thalidomide, and rituximab. First-line treatment for patients without hematologic malignancy (16 of 26) was corticosteroids alone (6 of 16) or associated with an alkylating agent (5 of 16).

Symptomatic treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or both was given to all patients.

Evolution to end-stage renal disease was observed in six patients after a mean delay of 45 months. Two of these

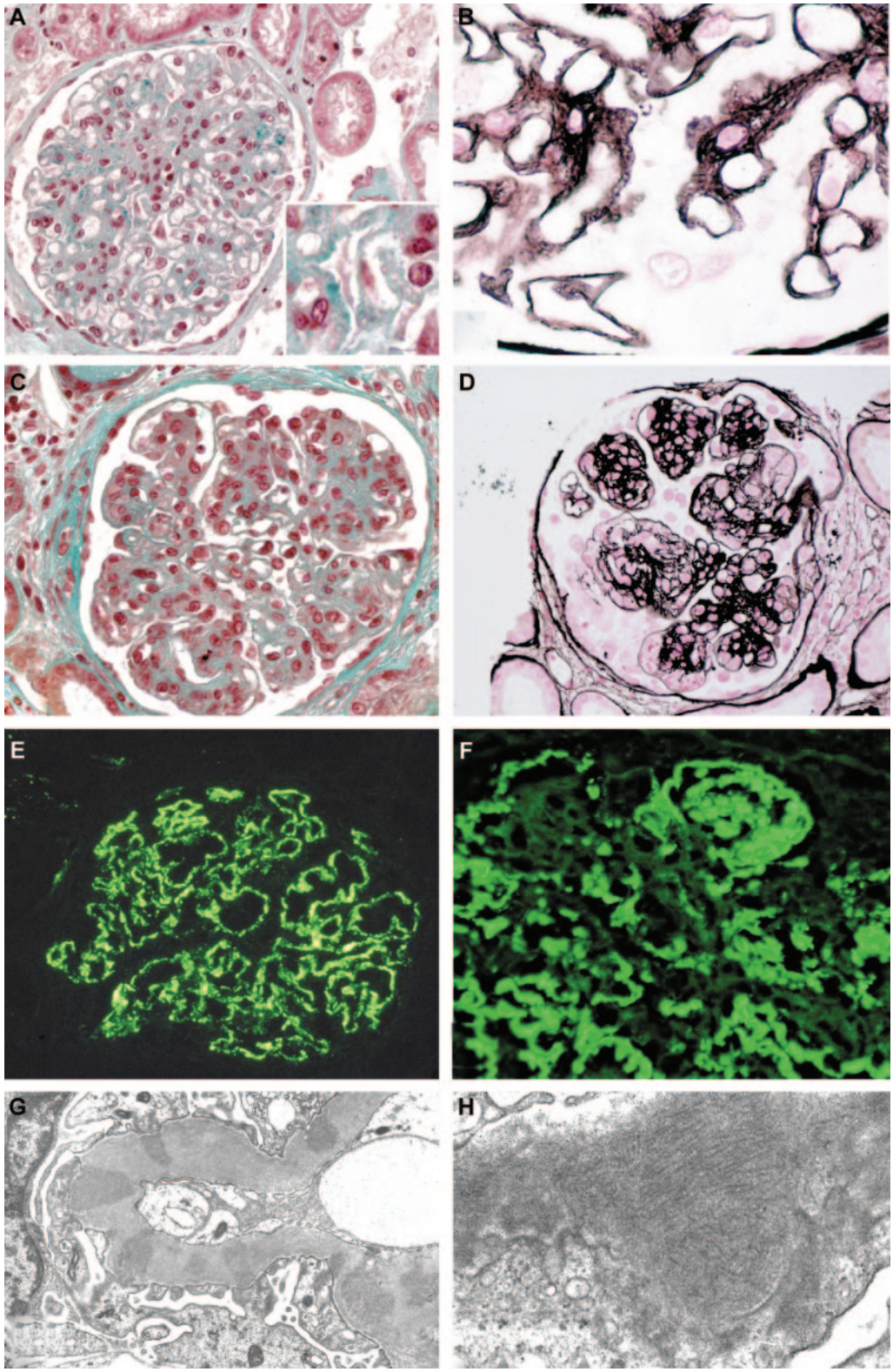

Figure 1. | Light microscopy findings in membranous nephropathy (MN) showing immune deposits on the external side of the glomerular basement membrane with frequent mesangial hypertrophy (A, Masson trichrome stain); the deposits have irregular size (inset of A) and are embedded in basement membrane expansions (B, Jone methenamine stain [JMS]). In patients with membranoproliferative pattern, light microscopy shows proliferation of mesangial cells (C, Masson trichrome stain) and double contours (D, JMS stain). By immunofluorescence, parietal granular IgG deposits in (E) MN are different from the more diffuse pattern seen in (F) membranoproliferative glomerulonephritis (MPGN). Ultrastructural studies found that most patients have granular, nonorganized deposits in the subepithelial (G) or subendothelial spaces, whereas in some patients, the deposits show microtubular substructure (H), as described previously in immunotactoid GN.

Table 2. Renal pathology, hematological disorder, treatment, and outcome of the patients

Patients	GN Type	Glomerular Deposits			Hematological Malignancy	Serum M-Spike	Initial Treatment	Outcome	Delay to Relapse (months)	Second-Line Treatment	Outcome
		Subclasses	κ/λ	Electron Microscopy							
1	MPGN	–	κ	–	–	IgGκ	CS	ESRD	–	–	–
2	MPGN	IgG1	κ	Nonorganized	–	IgGκ	CYC, CS, AZA	CR	–	–	–
3	MPGN	IgG3	κ	–	–	–	CYC, CS, AZA	CR	36	RTX, CS	CR
4	MPGN	IgG3	κ	Nonorganized	MM	IgG3κ	CYC, CS	ESRD	60	Thali, CS	ESRD
5	MPGN	IgG3	κ	–	–	–	CS	NR	–	–	–
6	MPGN	IgG3	κ	–	–	–	CS	NR	48	CS, MMF	NR
7	MPGN	IgG3	κ	Nonorganized	NHL	–	RTX, CS	CR	–	–	–
8	MPGN	IgG3	κ	–	–	–	RTX	CR	–	–	–
9	MPGN	–	λ	–	NHL	IgGλ	RTX, CHOP	CR	–	–	–
10	MPGN	IgG4	κ	–	–	–	None	ESRD	–	–	–
11	MPGN	IgG3	λ	Nonorganized	NHL	IgGλ	CHOP	NR	8	CS, MMF	NR
12	MPGN	IgG3	κ	Nonorganized	–	–	CS	CR	24	RTX	CR
13	MN	IgG1	κ	–	–	IgGκ	CYC, CS, AZA	CR	–	–	–
14	MN	IgG2	κ	Organized	CLL	–	None	Death	–	–	–
15	MN	–	κ	–	–	–	–	–	–	–	–
16	MN	IgG1	κ	Nonorganized	–	–	CS	ESRD	–	–	–
17	MN	–	κ	–	–	–	None	ESRD	–	–	–
18	MN	IgG1	λ	Nonorganized	MM	IgGλ	M, CS	CR	60	Thali, CS	CR
19	MN	IgG1	κ	Nonorganized	CLL	–	CYC, Fluda	CR	–	–	–
20	MN	IgG3	κ	Nonorganized	–	–	Chloramb, CS	CR	–	–	–
21	MN	IgG1	λ	–	–	–	None	ESRD	–	–	–
22	MN	IgG1	κ	–	–	–	None	CR	36	CS	CR
23	MN	–	κ	Organized	CLL	IgGκ	CHOP, Chloramb	NR	12	M, CS	NR
24	MN	IgG1	λ	Organized	CLL	–	CHOP, Fluda	CR	–	–	–
25	MN	IgG2	κ	Nonorganized	–	–	RTX	CR	–	–	–
26	MN	IgG3	κ	Nonorganized	–	–	RTX	PR	–	–	–

MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; CS, corticosteroids; CYC, cyclophosphamide; AZA, azathioprine; RTX, rituximab; CHOP, cyclophosphamide, adriamycine, vincristin, prednisone; M, melphalan; Chloramb, chlorambucil; Fluda, fludarabine; Thali, thalidomide; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; CLL, chronic lymphoid leukemia; CR, complete remission; PR, partial remission; NR, nonremission.

patients (patients 16 and 17) required renal transplantation with recurrence of the glomerular disease on the allograft for one. CR of the nephrotic syndrome was obtained in 13 patients (54%). In all of these patients, remission of nephropathy was reached only after disappearance of the circulating M-spike. Absence of renal remission was mainly observed among patients who were diagnosed at a late stage of chronic kidney disease, with elevated serum creatinine levels and presence of extensive fibrosis on the renal biopsy. Presence of an identified hematologic malignancy was not associated with a worse renal outcome, and CR of nephropathy was obtained in five of nine patients with myeloma, CLL, or lymphoma.

When considering the histologic pattern, patients with MPGN or with MN had the same prognosis. CR or PR was obtained in 6 of 12 patients with MPGN and 8 of 14 patients with monoclonal MN. Response to treatment was not associated with any clinical or laboratory feature, such as age, presence of malignancy, and level of proteinuria. The only nonstatistically significant differences between responders and nonresponders was the initial eGFR (61 ± 39 *versus* 41.1 ± 21 ml/min per 1.73 m^2, respectively; $P = 0.16$) and the degree of chronic lesions on the renal biopsy, such as percentage of glomerulosclerosis (12% *versus* 21%, $P = 0.2$) or the presence of severe vascular lesions (28% *versus* 63%, $P = 0.06$).

Rituximab was used in combination with other chemotherapies in two patients with low-grade lymphoma or alone in five patients with no malignancy as first-line treatment ($n = 3$) or as a second-line treatment ($n = 2$) after a relapse of the nephrotic syndrome. All seven patients received four weekly 375-mg/m^2 doses of rituximab and one patient received two maintenance doses 8 and 14 months after the initial treatment.

The mean follow-up after rituximab treatment was 24 months. In five of these patients, CR of the nephrotic syndrome was obtained after a mean delay of 9 months (4 to 24) after rituximab initiation. The two other patients showed PR with significant reduction of proteinuria, normalization of the serum albumin level, and stabilization of renal function. Evolutions of proteinuria, serum albumin, and eGFR are shown in Figure 2. Only one patient relapsed 44 months after initial treatment. Rituximab was not repeated because of severe deterioration of renal function and marked fibrosis on control biopsy.

The excellent results with rituximab therapy (five CR, two PR, one relapse) are very encouraging when compared with the results of corticosteroids alone (two CR, one PR, three NR, two relapses) or those of alkylating-agent-based schemes (seven CR, three PR, one NR, five relapses). Rituximab offers a much better tolerance profile than classic chemotherapies. In this series, three patients treated with alkylating agents presented severe infection and one developed myelodysplasic syndrome several years later. Among patients treated with rituximab alone, no major infectious complications have been observed to date.

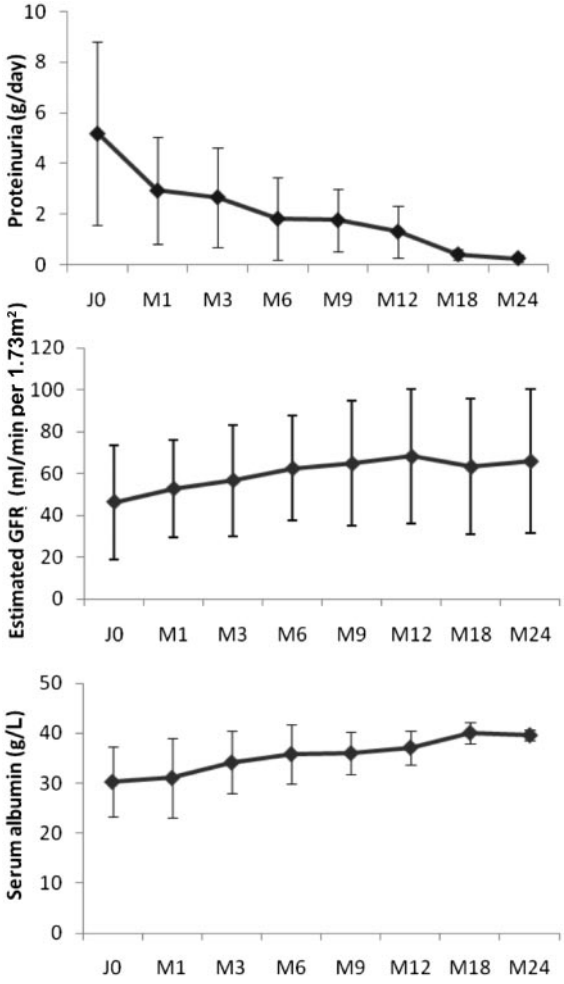

Figure 2. | Evolution of proteinuria, estimated GFR, and serum albumin after rituximab treatment. M, month.

Discussion

GN associated with monoclonal deposits of intact Ig is less common than diseases such as AL amyloidosis or light- or heavy-chain deposition diseases that are due to deposition of fragments of a monoclonal component. Nevertheless, several recent reports have underlined the fact that monoclonal entire IgG and IgM can cause nephrotic or nephritic syndromes and lead to renal failure in patients presenting with plasma cell dyscrasia or lymphoproliferative disease or without overt malignancy (8,9). Monoclonal cryoglobulins can trigger MPGN with intracapillary microthrombi and macrophagic infiltration (3,9), but monoclonal proliferative GN and MN can also be observed in patients with no detectable cryoglobulinemia and no hypocomplementemia (4,5,7,8,10,11). To obtain further insight into those glomerulopathies, we have reviewed the cases of 26 patients with noncryoglobulinemic GN and monoclonal IgG deposits recruited over 28 years in three nephrology departments.

The main limitation of this retrospective study is the lack of EM examination in 12 of 26 patients. This technique could allow the exact classification of all of these patients as either proliferative GN with monoclonal nonorganized IgG deposits or immunotactoid GN associated with microtubular deposits. Nevertheless, we decided to include all patients with glomerular disease associated with monoclonal IgG deposits only on the basis of light and immunofluorescence study because we think that the etiology,

prognosis, and treatment of all of these histologic subtypes may not differ according to their ultrastructural pattern. On the other hand, the EM study of a large subgroup of this series gives us some useful information about the relative frequency of each subtype, showing that proliferative GN (11 of 14) is much more frequent than immunotactoid GN (3 of 14).

Three major observations were made. First, the pattern of glomerular lesions is limited to MPGN and MN, which each accounts for approximately half of the cases. Second, there is a striking relationship between the type of glomerulopathy and the subclass of the deposited Ig. Third, rituximab appears to be a very promising drug, including in the patients without malignancy.

One of the important points shown by the immunofluorescence studies of our patients is the striking correspondence between the localization of the IgG deposits, defining either MPGN or MN histologic patterns, and the subclass of the monoclonal IgG found in the deposits. The predominance of IgG3 subclass in type 1 cryoglobulinemia (3) and in proliferative GN with monoclonal IgG deposits has already been reported. According to Nasr *et al.* (8), IgG3 was found in 21 of 32 patients with proliferative GN with monoclonal IgG. In our series, most patients (80%) with MPGN had associated IgG3 deposits. Classic MPGN is triggered by deposition of immune complexes in the mesangium and the glomerular capillaries, activating the complement cascade and recruiting inflammatory cells such as macrophages and lymphocytes. In monoclonal IgG3-associated MPGN, there is no evidence for an antigen-antibody immune complex, either circulating or formed *in situ*. According to several authors, this rather uncommon serum subclass of human IgG (mean normal adult level, 0.42 mg/ml; range 0.18 to 0.80 mg/ml) is the most nephritogenic because of its ability to aggregate in the glomerular capillary via a specific Fc-Fc interaction. IgG3 is also the most positively charged human IgG, favoring its affinity toward the anionic sites of the glomerular membrane (12,13). This high avidity of IgG3 for the glomeruli may also explain the fact that monoclonal components can remain undetectable in the serum of patients with proven monoclonal IgG3 kidney deposits.

On the other hand, >50% of the patients reported here present with an atypical form of monoclonal MN, similar to previously described patients (11,14,15). Interestingly, we show that most (64%) cases of monoclonal MN are due to IgG1 deposits, whereas IgG3 is rarely observed. These data confirm the observations of Bridoux *et al.* (5), who found that 5 of 10 patients with atypical MN due to monotypic Ig deposits had IgG1 subclass deposited in their glomeruli. The one patient from the Nasr series with membranous features also had IgG1 deposits. However, it is difficult to draw definitive conclusions about the propensity of this subclass for membranous deposits because it is the most frequent Ig subclass found in monoclonal gammopathies (16). Nevertheless, one of our previous reports (17) supports the hypothesis that, in contrast to classic MN, the deposited Ig may not be directed against a local antigen but instead may precipitate because of peculiar physicochemical properties.

This study also reveals some new therapeutic possibilities in this rare type of glomerulopathy. Of course, all patients who present with a well defined, severe hematologic malignancy (such as MM and high-grade NHL associated with a monoclonal compound) must be treated according to the standard chemotherapy protocols, including newly introduced drugs such as thalidomide, bortezomib, or rituximab. Our study confirms that if the treatment permits sustained hematologic remission and suppression of the circulating monoclonal IgG, then the renal disease can disappear. When the hematologic workup establishes the presence of a low-tumoral mass plasma cell dyscrasia or a low-grade lymphoproliferative disease, nephrologists have to convince hematologists that, as in AL amyloidosis, the treatment of the otherwise "benign" neoplasm is mandatory to hamper the renal disease.

However, for patients without overt malignancy, rituximab may be the optimal therapeutic choice. Indeed, our study confirms previously published data, showing that treatment with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers or corticosteroids alone is not sufficient to achieve long-term remission. Alkylating agents have proved their efficacy, but they have several immediate and long-term side effects that limit their use. On the other hand, rituximab has a very favorable benefit-to-tolerance ratio in this subgroup of patients. This treatment has been proposed in several kidney diseases such as mixed hepatitis-C-related cryoglobulinemic MPGN (18) or idiopathic MN (19). In the series reported by Nasr (8), two of four patients with MPGN and monoclonal IgG deposits who received this B cell–depleting drug experienced PR. Three other reports on monoclonal MPGN or immunotactoid GN (10,20,21) also suggest that rituximab can be beneficial in this setting. In our series, five of seven patients with either MPGN or MN showed CR and two experienced a good-quality PR with no major side effects. Further studies are necessary to define which patients should be treated with this new drug and what should be the best therapeutic scheme.

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Disclosures

None.

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