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Proliferative glomerulonephritis with monoclonal IgG deposits: A distinct entity mimicking immune-complex glomerulonephritis

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Proliferative glomerulonephritis with monoclonal IgG deposits: A distinct entity mimicking immune-complex glomerulonephritis.

Background. Renal disease related to the deposition of monoclonal immunoglobulins containing both heavy and light chains can occur in type 1 cryoglobulinemia, Randall type light and heavy chain deposition disease (LHCDD), and immunotactoid glomerulonephritis. We report a novel phenotype of glomerular injury that does not conform to any of the previously described patterns of glomerular involvement by monoclonal gammopathy.

Methods. Ten cases of unclassifiable proliferative glomerulonephritis manifesting glomerular monoclonal immunoglobulin G (IgG) deposits were identified retrospectively from the archives of the Renal Pathology Laboratory of Columbia University over the past 3 years (biopsy incidence 0.21%).

Results. The monoclonal immunoglobulins formed granular electron dense deposits in mesangial, subendothelial, and subepithelial sites, mimicking ordinary immune complex–mediated glomerulonephritis and producing a diffuse endocapillary proliferative or membranoproliferative glomerulonephritis. However, by immunofluorescence, the deposits were monoclonal, staining for a single light chain isotype and a single gamma subclass (including two IgG1κ, one IgG1λ, one IgG2λ, four IgG3κ, and one IgG3λ). All cases stained for the three constant domains of the gamma heavy chain (CH1, CH2, and CH3), suggesting deposition of a nondeleted immunoglobulin molecule. Tissue fixation of complement was observed in 90% of cases, and 40% of patients had hypocomplementemia. Clinical presentations included renal insufficiency in 80% (mean serum creatinine 2.8 mg/dL, range 0.9 to 8.0), proteinuria in 100% (mean urine protein 5.8 g/day; range 1.9 to 13.0), nephrotic syndrome in 44%, and microhematuria in 60%. A monoclonal serum protein with the same heavy and light chain isotype as that of the glomerular deposits was identified in 50% of cases (including three IgGκ and two IgGλ); however, no patient had clinical or laboratory features of type 1 cryoglobulinemia. No patient had overt myeloma or lymphoma at presentation or over the course of follow-up (mean 12 months).

Conclusion. Glomerular deposition of monoclonal IgG can produce a proliferative glomerulonephritis that mimics immune-complex glomerulonephritis by light and electron microscopy. Proper recognition of this entity requires confirmation of monoclonality by staining for the gamma heavy chain subclasses.

Most forms of renal disease associated with monoclonal gammopathy result from the deposition of monoclonal immunoglobulins or their subunits in one or more renal compartments, including glomeruli, tubules, interstitium, and vessels. The majority of monoclonal components depositing in the renal parenchyma are actually monoclonal immunoglobulin light chains, leading to Randall type light chain deposition disease (LCDD), AL amyloidosis, or myeloma cast nephropathy. Deposition of monoclonal proteins containing both heavy and light chains is far less common and may manifest as type 1 cryoglobulinemic glomerulonephritis [1], Randall type light and heavy chain deposition disease (LHCDD) [2], immunotactoid glomerulonephritis [3, 4], and rarely fibrillary glomerulonephritis [3, 5]. In type 1 cryoglobulinemia, a membranoproliferative glomerulonephritis (MPGN) with macrophage infiltration is the most characteristic histologic pattern and the deposits are typically, but not invariably, organized into fibrillary or microtubular structures at the ultrastructural level. LHCDD is characterized by the presence of nodular sclerosing glomerulopathy by light microscopy, monoclonal linear staining of glomerular and tubular basement membranes for a single heavy chain and a single light chain by immunofluorescence, and nonfibrillar, punctate electron dense deposits involving glomerular and tubular basement membranes by electron microscopy. The hallmark of immunotactoid glomerulonephritis is the presence of highly organized nonamyloidotic microtubular

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deposits, usually of >30 nm in diameter, with hollow cores and parallel stacking. Very rarely, non-Randall type and nonorganized glomerular monoclonal immunoglobulin deposition that does not conform to any of the previous categories may occur [6–9].

Herein, we describe a series of ten patients with a novel form of glomerulonephritis related to monoclonal IgG deposition that could not be assigned to any of the established categories of glomerular involvement by dysproteinemia. By electron microscopy, the glomerular deposits appeared primarily granular, resembling ordinary immune complex deposits. However, by immunofluorescence, they contained immunoglobulins restricted to a single immunoglobulin class, a single immunoglobulin subclass, and a single light chain, consistent with monoclonal proteins. Monoclonal IgG was detectable in the serum of 50% of patients; however, no patient had overt myeloma, lymphoma or type 1 cryoglobulinemia. Proper recognition of this rare entity and differentiation from immune complex-mediated glomerulonephritis requires confirmation of the monoclonal nature of the glomerular deposits by staining for subclasses of the gamma heavy chain.

METHODS

Ten cases of unclassifiable glomerulonephritis with monoclonal IgG deposition were identified retrospectively from the archives of 4650 native renal biopsies accessioned by the Renal Pathology Laboratory of Columbia University College of Physicians and Surgeons from January 2000 to February 2003, for a biopsy incidence of 0.21%. By comparison, the biopsy incidences of AL amyloidosis and Randall type monoclonal immunoglobulin deposition disease [including LCDD, LHCDD, and heavy chain deposition disease (HCDD)] over the same 3-year time period were 1.66% and 0.52%, respectively.

Inclusion criteria included renal biopsy findings of glomerulonephritis with all of the following: (*1*) immune deposits staining positive for gamma heavy chain (IgG), with negativity for alpha (IgA) and mu (IgM) heavy chains, indicating restriction to a single immunoglobulin class, (*2*) positive staining for a single gamma (IgG) subclass (IgG1, IgG2, IgG3, or IgG4), (*3*) positive staining for a single light chain isotype (kappa or lambda), indicating monoclonality, (*4*) predominantly granular electron-dense deposits in mesangial, subendothelial, and/or subepithelial locations by electron microscopy, resembling immune complex glomerulonephritis, and (*5*) no clinical or laboratory evidence of cryoglobulinemia. Cases with clinicopathologic features of amyloidosis, Randall type monoclonal immunoglobulin deposition disease, fibrillary glomerulonephritis, and immunotactoid glomerulonephritis were excluded.

All ten renal biopsies were processed by standard techniques of light microscopy, immunofluorescence, and electron microscopy. For each case, 11 glass slides were prepared and stained with hematoxylin and eosin, periodic acid-Schiff (PAS), trichome, and Jones methenamine silver (JMS). Ultrastructural evaluation was performed using a JEOL 100S electron microscope (Tokyo, Japan).

Immunofluorescence was performed on 3 μm cryostat sections using polyclonal fluorescein isothiocyanate (FITC)-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, and albumin (Dako Corporation, Carpinteria, CA, USA). The intensity of immunofluorescence staining was graded on a scale of 0 to 3+. Determination of the IgG subclass was performed on 3 μm cryostat sections using monoclonal FITC-conjugated antibodies to IgG1 (clone 8c/6–39), IgG2 (clone HP6014), IgG3 (clone HP6050), and IgG4 (clone HP6023) (The Binding Site, Birmingham, UK). Frozen sections were also stained with monoclonal antibodies to epitopes of the constant domains of IgG heavy chains (CH1, clones TM1 and HP6044; CH2, clones G7C and HP6018; and CH3, clone HP6017) (provided by Dr. Margaret Goodall, Birmingham, UK, and the Centers for Disease Control and Prevention, Atlanta, GA), followed by FITC-conjugated sheep antimouse secondary antibody (Sigma-Aldrich, St. Louis, MO, USA). Two cases of lupus nephritis were used as positive controls. Glomerular macrophages were quantitated by CD68 immunostain (diluted 1:100) (Dako) using an avidin biotin immunoperoxidase technique.

Patients' medical records were reviewed for age, gender, clinical presentation, parameters of renal function, presence of serum and urine monoclonal immunoglobulin, treatment, and outcome. The following clinical definitions were applied: renal insufficiency, serum creatinine >1.2 mg/dL; nephrotic range proteinuria (NRP), 24-hour urine protein >3 g/day; hypoalbuminemia, serum albumin <3.5 g/dL; nephrotic syndrome, NRP, hypoalbuminemia, and peripheral edema; hematuria, >5 red blood cells per high power field on microscopic examination of the urinary sediment; and hypertension, blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic. A standard definition for multiple myeloma was applied [10]. Cryoglobulin measurements, performed in all patients at least twice prior to initiation of therapy, were obtained by blood collection in prewarmed containers at 37°C until clotted, centrifugation at 37°C for the separation of serum from cells, and storage of serum at 4°C for at least 3 days.

RESULTS

Clinical features

The clinical features are summarized in Table 1. The cohort consisted of five males and five females, all Caucasians, with a mean age of 58 years (range 44 to

Table 1. Clinical data

Patient number	1	2	3	4	5	6	7	8	9	10
Age/gender/race	58/M/C	53/F/C	53/F/C	59/M/C	68/F/C	63/F/C	52/F/C	51/M/C	78/M/C	44/M/C
Serum creatinine *mg/dL*	5.5	1.9	2	2.8	1.6	0.9	2.2	8.0	1.7	1.2
Proteinuria *g/24 hours*	3.5	7.8	13	1.9	9	2	7.5	NA	2.7	5
Serum albumin *g/dL*	2.4	3.2	2.7	3.3	3.4	2.7	2.6	2.4	4.2	3.2
Edema	Absent	++	Absent	Absent	++++	Absent	++	++	Absent	+
Serum cholesterol *mg/dL*	Unknown	231	225	250	Unknown	247	288	Unknown	150	325
Microhematuria	Present	Present	Absent	Absent	Present	Absent	Present	Absent	Present	Present
Serum paraprotein	IgGλ	Negative	IgGλ	Negative	IgGκ	IgGκ	Negative	IgGκ	Negative	Negative
Urine paraprotein	Negative	Negative	IgGλ	Negative	IgGκ	IgGκ	Negative	IgGκ	Negative	Negative
Bone marrow Bx	Not done	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Not done
Hypocomplementemia	Yes	Yes	No	Yes	Yes	No	No	No	No	No
Associated medical conditions	Sinusitis	None	HTN, obesity	HTN, CAD	HTN	HTN	None	Carcinoma of anus	None	HTN
Treatment	Prednisone	ACE inhibitor	Prednisone/ thalidomide	Prednisone	ACE inhibitor	ACE inhibitor	Prednisone/ cytoxan	Prednisone	ACE inhbitor/ ASA	ACE inhibitor/ MMF/CSA
Length of postbiopsy follow-up *months*	8	4	10	12	14	2	4	12	NA	52
Follow-up creatinine *mg/dL*	1.2	0.9	3.5	HD/expired	1.7	0.9	2.6	HD	NA	1.9
Follow-up proteinuria	Uprotein/ creatinine <1	NA	2.2 g/day	NA	1.19 g/day	NA	NA	NA	NA	3.95 g/day

Abbreviations are: M, male; F, female; C, Caucasian; HTN, hypertension; CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ASA, aminosalicylic acid; MMF/CSA, mycophenolate mofetil/cyclosporine; NA, not available; HD, hemodialysis.

78 years). At the time of presentation, eight of ten patients (80%) had renal insufficiency. Mean serum creatinine for the entire cohort was 2.8 mg/dL (range 0.9 to 8.0 mg/dL). In all nine patients tested, there was evidence of proteinuria, including four with full nephrotic syndrome, two with NRP in the absence of full nephrotic syndrome, and three with subnephrotic proteinuria. The mean 24-hour urine protein was 5.8 g/day (range 1.9 to 13.0 g/day) and the mean serum albumin was 3 g/dL (range 2.4 to 4.2 g/dL). Five patients exhibited peripheral edema and six had microhematuria.

On serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), four patients had monoclonal (M) spikes in both the serum and urine, and one patient had an M spike detectable in the serum only. In these five cases, the monoclonal proteins in both serum and urine had the same heavy and light chain isotype as that of the monoclonal immunoglobulin deposited in the kidney, including three IgGκ and two IgGλ. The monoclonal protein comprised 10% of the total urine protein in patient 5; the percentage monoclonal protein was not available in the others. No monoclonal protein was detected in the serum or urine of the remaining five patients despite the use of the sensitive methods of immunoelectrophoresis and immunofixation. Immunoblots were not performed**.** Bone marrow examination, performed in eight patients (including all those with serum or urine paraproteins), revealed <5% plasma cells. Results of skeletal surveys were normal in all patients. None of the patients had lymphadenopathy, hepatosplenomegaly, or any clinical evidence of B-cell lymphoma. Thus, no patient met criteria for myeloma or other hematologic malignancy. Cryoglobulin titers were negative on at least two determinations in all patients. In addition, none of the patients had any systemic manifestation of cryoglobulinemia, namely palpable purpura, arthralgias, arthritis, skin ulcers, Raynaud's phenomenon, or peripheral neuropathy. Four patients were hypocomplementemic (reduced C3 and C4 in one patient, reduced C4 alone in two, and reduced C3 alone in one). The following serologies were negative in all patients: antinuclear antibody (ANA), hepatitis B surface antigen, and hepatitis C antibody. Rheumatoid factor, tested in eight patients, was negative.

Pathologic findings

The renal biopsy findings are detailed in Table 2. Glomerular sampling for light microscopy ranged from 2 to 29 glomeruli (mean 14), and global glomerulosclerosis involved a mean of 18% of glomeruli (range 0% to 59%). All patients exhibited proliferative glomerulonephritis, although the histologic features were heterogeneous. Diffuse endocapillary proliferative glomerulonephritis (DPGN) was the major light microscopic pattern, observed in five cases (Fig. 1A). This pattern was characterized by marked endocapillary hypercellularity and leukocyte infiltration causing luminal occlusion. Of these five patients, four had associated segmental membranoproliferative features (patients 2, 3, 8, and 9), two had mild to moderate neutrophil infiltration (patients 2 and 3), and one had severe crescentic features with over 75% crescent formation (patient 8). Of note, no crescents were identified in the other nine patients. Four patients showed a predominant pattern of MPGN characterized by diffuse and global mesangial interposition and duplication of glomerular basement membranes associated with mesangial hypercellularity and focal macrophage infiltration (Fig. 1B). One of these cases displayed associated membranous features, resembling MPGN type 3 (patient 10). A predominantly membranous glomerulonephritis pattern with segmental membranoproliferative features was seen in one patient (patient 6) (Fig. 1C). The mean number of infiltrating macrophages per glomerulus by CD68 immunostain was seven for DPGN, eight for MPGN, and one for membranous glomerulonephritis.

The degree of cortical scarring in the form of tubular atrophy and interstitial fibrosis ranged from mild (six patients) to moderate (two patients) to severe (two patients). Interstitial inflammation ranged from mild (five patients) to moderate (four patients) to severe (one patient). Arterio- and arteriolosclerosis ranged from absent (two patients) to mild (five patients) to moderate (three patients).

Two patients had additional unique features. In a single patient (patient 3), vessels were expanded by Congo red–positive, eosinophilic material indicative of coexistent amyloid that was restricted to the vascular compartment, with no detectable amyloid involving glomeruli. The additional diagnosis of primary amyloidosis, restricted to blood vessels, was confirmed by the immunofluorescence finding of "smudgy" vascular deposits that stained solely for lambda and the ultrastructural finding of randomly oriented fibrils measuring 12 to 14 nm in diameter. In patient 4, there was also arteriolar deposition of glassy, eosinophilic, Congo red–negative intimal material staining for IgGλ, consistent with vascular paraprotein deposits, which were associated with mild arteriolitis.

By immunofluorescence, the texture of the deposits was granular in all cases, with the exception of patient 5 where the deposits appeared semilinear (Table 2). In all patients, IgG was the only immunoglobulin deposited (intensity 1 to 3+) (Fig. 1D). All patients had light chain isotype restriction, including six cases with sole positivity for kappa (intensity 1 to 3+) and four with sole positivity for lambda (intensity 3+) (Fig. 1E and F). The deposits localized to the glomerular capillary wall and mesangium (seven patients), or to the glomerular capillary wall alone (three patients). In a similar distribution to the IgG deposits, glomerular deposits of C3 (intensity 1 to 3+) were

Table 2. Renal biopsy findings

Patient number	1	2	3	4	5	6	7	8	9	10
Light microscopy										
No. glomeruli	31	19	14	13	2	15	7	9	29	4
No. sclerotic glomeruli	2	1	2	6	0	4	0	2	17	0
Pattern of glomerulonephritis	DPGN	DPGN	DPGN	MPGN	MPGN	MGN	MPGN	DPGN	DPGN	MPGN
Tubular atrophy and interstitial fibrosis	Mild	Mild	Severe	Mild	Mild	Moderate	Moderate	Mild	Severe	Mild
Interstitial inflammation	Mild	Mild	Moderate	Mild	Mild	Moderate	Moderate	Severe	Moderate	Mild
Vascular disease	Mild	Mild	Mild	Moderate	Absent	Mild	Absent	Moderate	Moderate	Mild
Immunofluorescence ¶										
IgG	3+ MES/CW	3+ CW	3+ MES/CW	2+ MES/CW	1+ MES/CW	3+ CW	3+ MES/CW	2+ MES/CW	1+ MES/CW	3+ CW
IgG subtype	IgG1	IgG3	IgG2	IgG3	IgG1	IgG1	IgG3	IgG3	IgG3	Not done
C3	—	3+ CW	3+ MES/CW	3+ MES/CW	2+ MES/CW	2+ CW	2+ MES/CW	3+ MES/CW	1+ MES/CW	3+ CW
C1	—	1+ CW	—	—	—	—	2+ MES/CW	—	—	2+ CW
Kappa	—	3+ CW	—	—	1+ MES/CW	3+ CW	3+ MES/CW	2+ MES/CW	+1 MES/CW	—
Lambda	3+ MES/CW	—	3+ MES/CW	3+ MES/CW	—	—	—	—	—	3+ CW
Electron microscopy ¶										
Mesangial deposits	3+	—	3+	1+	2+	1+	3+	2+	1+	2+
Subendothelial deposits	3+	3+	2+	2+	2+	1+	2+	3+	2+	2+
Subepithelial deposits	1+	—	2+	1+	—	2+	-	1+	1+	2+
% Foot process fusion	50	65	70	60	70	90	95	80	75	80

Abbreviations are: DPGN, diffuse proliferative (mesangial and endocapillary) glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; MGN, membranous glomerulonephritis; MES, mesangial; CW, glomerular capillary wall.

¶ For immunofluorescence and electron microscopy, deposits were quantitated on a scale of 0 to 3+.

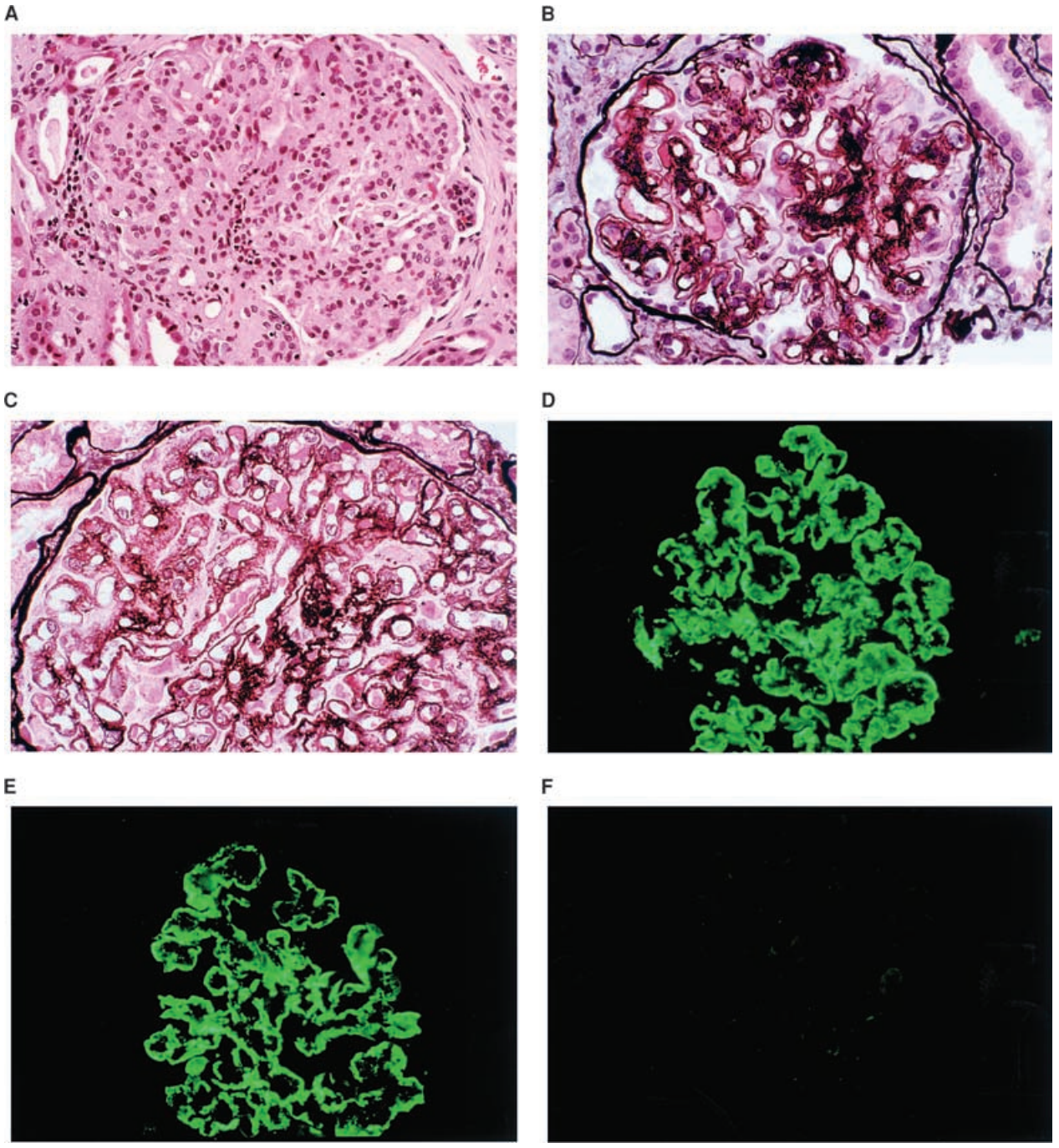

Fig. 1. Light microscopic findings and routine immunofluorescence findings. (*A*) The most common histologic pattern is endocapillary proliferative glomerulonephritis with accentuated glomerular lobularity. There is global narrowing or occlusion of the glomerular capillary lumina by endocapillary cells, including focal infiltrating mononuclear and polymorphonuclear leukocytes (patient 3) (hematoxylin and eosin, ×200). (*B*) An example of membranoproliferative glomerulonephritis (MPGN) with widespread duplication of glomerular basement membrane, forming double contours. Subendothelial eosinophilic deposits are visible in some capillaries (patient 7) (Jones methenamine silver, ×400). (*C*) The patient with predominantly membranous pattern shows widespread thickening of the glomerular capillary walls by subepithelial and intramembranous deposits separated by basement membrane spikes. Some of the deposits are overlaid by neomembrane, producing chain-like thickenings of the glomerular capillary walls (patient 6) (Jones methenamine silver, ×620). By routine immunofluorescence, patient 2 shows strong staining for IgG (*D*) and kappa (*E*), with negative lambda (*F*) (×400).

detected in nine patients, with deposits of C1q (intensity 1 to 3+) in three. IgM and IgA were negative in all patients. None of the cases had deposits involving tubular basement membranes or interstitium.

Immunofluorescence staining for IgG1-4 subclasses showed monotypic deposits in all nine patients studied, including three IgG1 (one IgG1λ and two IgG1κ), one IgG2λ, and five IgG3 (four IgG3κ and one IgG3λ)

(Fig. 2A to D). No patient had positivity for IgG4. Lupus nephritis controls showed usual polytypic staining (for IgG1, 2, 3, and 4). In all nine patients studied, staining for the constant domains of the gamma heavy chain revealed strong positivity for the CH1, CH2, and CH3 domains in the same distribution as the monoclonal IgG deposits (Fig. 2E to G). Regular staining for CH1, CH2, and CH3 was also observed in the lupus nephritis controls.

On ultrastructural analysis, the immune deposits were primarily mesangial and subendothelial (Table 2). Subepithelial deposits were identified in seven patients, but predominated in the single patient (patient 6) that had primarily membranous features by light microscopy. Eight patients had electron dense deposits with a finely granular texture throughout, without substructure (Fig. 3A). One of these cases contained focally fibrillar material typical of fibrin tactoids admixed with the more granular subendothelial deposits (patient 8). Of the remaining two patients, one patient (patient 3) had focal organization of the electron dense deposits into lattice-like arrays with a periodicity of 15 nm (Fig. 3B). The deposits in the other (patient 1) had a slightly variegated texture, suggesting an ill-defined substructure, but without evidence of well-developed microtubules or fibrils. The latter case was also remarkable for the unique feature of elongated crystalloid deposits within membrane-bound vesicles of the intraglomerular infiltrating monocytes (Fig. 3C). None of the patients showed deposits with annular-tubular substructures typical of cryoglobulinemic glomerulonephritis or punctate, ribbon-like deposits along the glomerular and tubular basement membranes characteristic of Randall type LHCDD.

Clinical outcome

Clinical follow-up was available for nine of ten patients and the mean follow-up period was 12 months (range 2 to 52 months). Six patients received immunosuppressive therapy, including steroids alone in three, steroids plus thalidomide in one, steroids plus cyclophosphamide in one, and mycophenolate mofetil plus cyclosporine in one. The remaining four patients received angiotensin-converting enzyme (ACE) inhibitor alone. Within the period of time with available follow-up, two patients had a significant decline in serum creatinine from 5.5 to 1.2 mg/dL and from 1.9 to 0.9 mg/dL (patients 1 and 2) and two had stable renal function (patients 5 and 6). This included one patient treated with prednisone and three treated solely with ACE inhibitor. In contrast, two patients became dialysis-dependent (patients 4 and 8) and three patients had increases in serum creatinine of 1.5, 0.4, and 0.7 mg/dL (patients 3, 7, and 10, respectively). In all four patients with follow-up urine protein quantitation, a decline in proteinuria was seen, although in two patients this was associated with progressive renal insufficiency. From these data, no conclusions can be drawn with respect to treatment and outcome. Over the course of follow-up, no patient developed myeloma or lymphoma.

DISCUSSION

Glomerulonephritis associated with monoclonal IgG deposits can be seen in type 1 cryoglobulinemia and in immunotactoid glomerulonephritis, two diseases that are usually associated with hematologic malignancies. In type 1 cryoglobulinemia, renal involvement is rare and is characterized pathologically by a pattern of MPGN [1]. In immunotactoid glomerulonephritis, a disease characterized by the presence of nonamyloidotic microtubular deposits (usually >30 nm in diameter), the most common light microscopic patterns are MPGN and DPGN [3].

Herein, we describe ten cases of glomerulonephritis associated with monoclonal IgG deposition. The main light microscopic patterns were DPGN and MPGN. By electron microscopy, the deposits were mainly granular, resembling immune complex deposits. None of the patients showed the microtubular deposits typical of immunotactoid glomerulonephritis, or the punctate, continuous deposits along the glomerular and tubular basement membranes typical of Randall type LHCDD. Type 1 cryoglobulinemic glomerulonephritis was unlikely based on the absence of any clinical and laboratory evidence of cryoglobulinemia as well as by the absence of deposits with characteristic annular-tubular or fibrillar substructure by electron microscopy. The monoclonal deposits included IgGκ in six cases and IgGλ in four. Monoclonal IgG with the same heavy and light chain isotype as that seen in the glomerular deposits was detected in the sera of five patients. The inability to identify a corresponding monoclonal protein in the others may relate to its presence at very low titers, below the level of detection by standard immunoelectrophoresis, or to rapid rates of tissue deposition [11]. Unfortunately, more sensitive immunoblots were not available in any case to confirm the identity of the serum and glomerular monoclonal immunoglobulins with respect to gamma subclass. None of our patients developed myeloma over the course of follow-up. Longer follow-up is needed to determine whether this entity represents a form of premyeloma, as has been reported for light chain Fanconi syndrome [12].

There are four reports of similar cases [6, 8, 9] [abstract; Bridoux F, et al, *J Am Soc Nephrol* 12:94A, 2001]. Alpers et al [6] described 11 patients with glomerulonephritis associated with renal immunoglobulin light chain or monoclonal immunoglobulin deposition. Immunofluorescence studies disclosed monoclonal IgGκ and C3 staining in six patients. Light and electron microscopic examination in these six patients showed a membranoproliferative pattern with mesangial hypercellularity, increased mesangial matrix, and mesangial interposition by light microscopy and granular subendothelial and mesangial deposits by

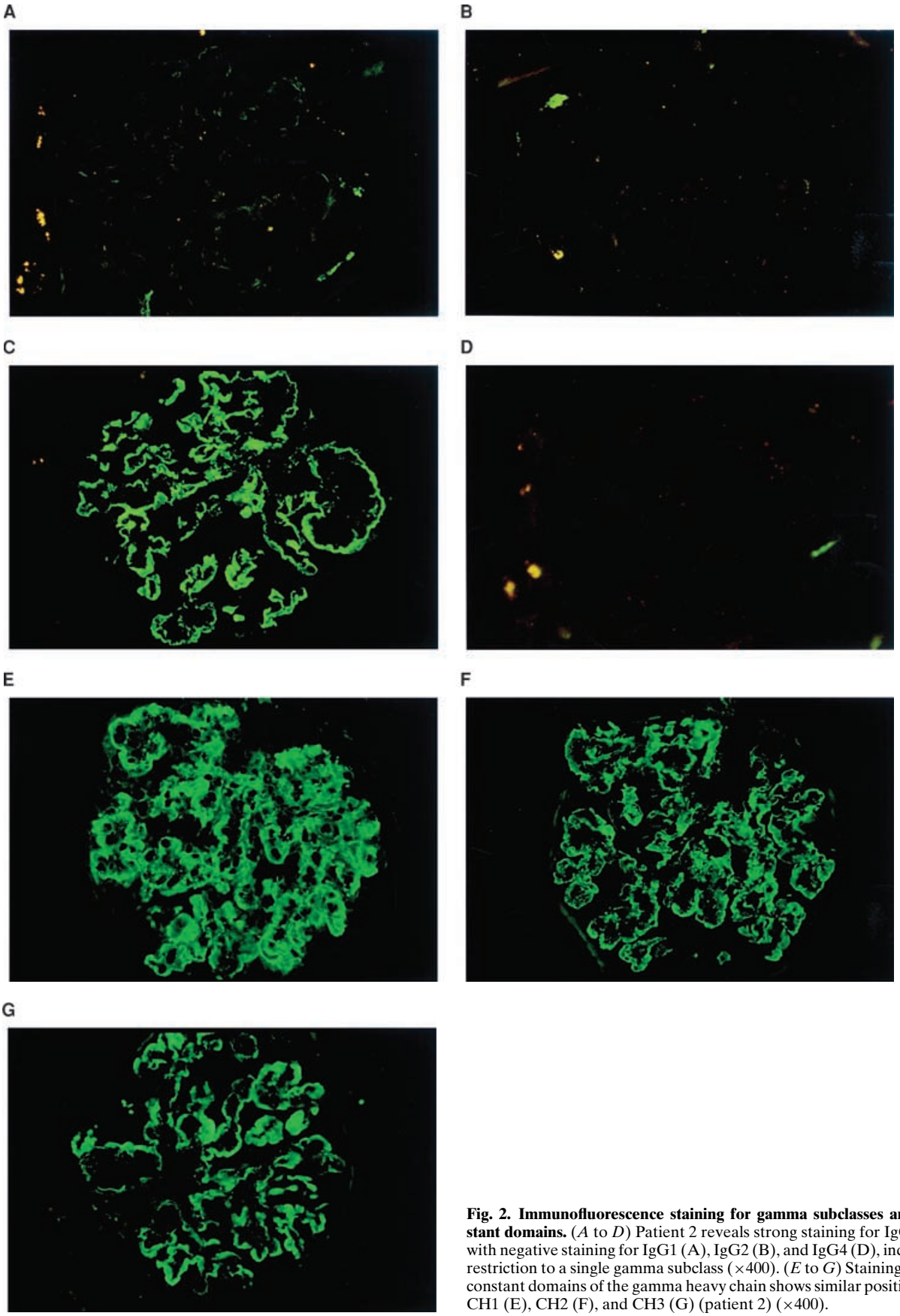

Fig. 2. Immunofluorescence staining for gamma subclasses and constant domains. (*A* to *D*) Patient 2 reveals strong staining for IgG3 (C), with negative staining for IgG1 (A), IgG2 (B), and IgG4 (D), indicating restriction to a single gamma subclass (×400). (*E* to *G*) Staining for the constant domains of the gamma heavy chain shows similar positivity for CH1 (E), CH2 (F), and CH3 (G) (patient 2) (×400).

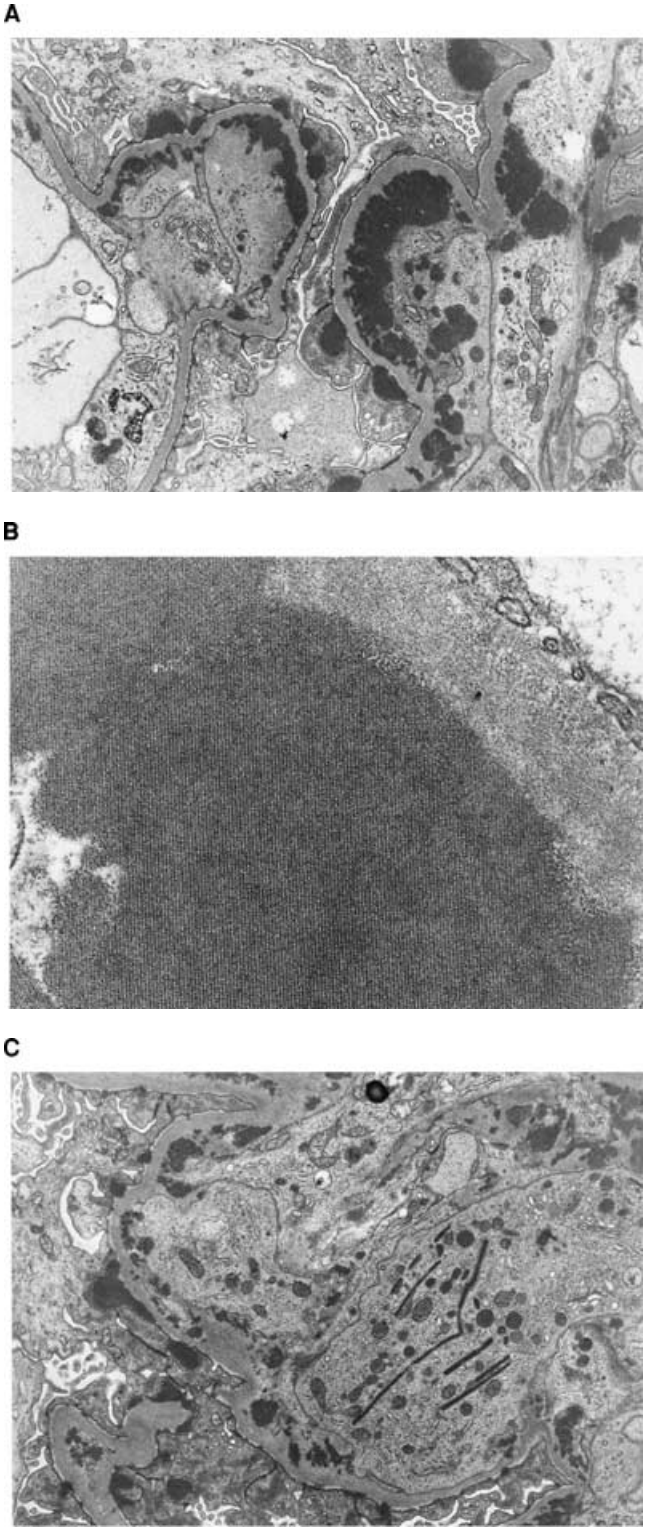

Fig. 3. Electron microscopic findings. (*A*) There are granular electron dense deposits in subendothelial and subepithelial locations, mimicking immune complex glomerulonephritis (patient 1).(×3000). (*B*) In patient 3, the glomerular deposits displayed a focal lattice-like substructure forming parallel linear arrays with 15 nm periodicity (×30,000). (C) In patient 1, the infiltrating glomerular macrophages contained focal intracellular crystals, however the extracellular electron dense deposits were granular and amorphous (×2000).

electron microscopy. Clinically, none of these six patients had detectable serum or urine monoclonal immunoglobulins and bone marrow examination in four patients was normal. Bridoux et al [abstract; Bridoux F, et al, *J Am Soc Nephrol* 12:94A, 2001] described five patients manifesting glomerulopathy with nonorganized, non-Randall type monoclonal immunoglobulin deposits, two of which were described in detail by Touchard [7]. Mean age was 54 ± 17 years and all presented with microhematuria and renal failure; nephrotic syndrome was present in 80%. Renal biopsy revealed atypical membranous, endocapillary proliferative, and membranoproliferative patterns. By immunofluorescence, the glomerular capillary wall deposits consisted of IgG3κ in two patients, IgG3λ in one, IgG2κ in one, and isolated lambda light chain in one. Corresponding monoclonal proteins were detected in serum or urine in three patients, two of which required immunoblotting. A unique case of hypocomplementemic MPGN associated with monoclonal lambda light chain dimers isolated from the serum and urine has also been described [9].

There have been other reports in the older literature of patients with proliferative glomerulonephritis associated with circulating monoclonal IgG, without associated cryoglobulin activity [13–16]. Because these reports lacked description of either electron microscopic or immunofluorescence examination or both, it is uncertain whether these cases represent Randall type monoclonal immunoglobulin deposition disease, immunotactoid glomerulopathy, or are similar to the cases reported herein.

IgG subclass analysis performed in nine of our patients confirmed that the deposits were monotypic (five IgG3, three IgG1, and one IgG2). Interestingly, a similar predominance of IgG3 was reported by Bridoux et al in three of five patients with glomerulopathy due to nonorganized, non-Randall type monoclonal immunoglobulin deposits [abstract; Bridoux F, et al, *J Am Soc Nephrol* 12:94A, 2001]. Hypocomplementemia was present in two of our patients with IgG3 subtype and two patients with IgG1 subtype, but not in the patient with IgG2 subtype. This may reflect the fact that IgG1 and IgG3 are the most effective IgG subclasses at complement activation [17]. Similarly, hypocomplementemia frequently complicates HCDD, a disorder in which the deposits are most commonly of the IgG1 or IgG3 subtype [2, 18] and may also occur in patients with immunotactoid glomerulopathy related to monoclonal IgG1 deposition [3]. Thus, we suspect that the mechanism of complement activation and resultant hypocomplementemia is analogous to that of HCDD, LHCDD, immunotactoid glomerulopathy, or type 1 cryoglobulinemia, disorders in which renal deposition of a paraprotein or whole immunoglobulin containing a gamma heavy chain is capable of complement activation in the absence of circulating immune complexes.

In contrast to the situation in HCDD [2, 18, 19], heavy chain disease (HCD) [20], and possibly LHCDD [8], no deletion of the CH1 domain was detected in our cases using epitope-specific monoclonal antibodies for the gamma heavy chain constant domains. In the case of HCDD, the lack of CH1 domain results in premature secretion of the truncated heavy chains from plasma cells prior to their assembly into the complete immunoglobulin molecule [19, 21]. The findings in our patients suggest that the monoclonal IgG is deposited as a complete immunoglobulin molecule with retention of immunoreactivity for both the heavy chain and light chain, and without detectable deletions in any of the constant domains of the gamma heavy chain. The lack of deletion of CH1 allows assembly of the complete immunoglobulin molecule by binding of the nascent heavy chain to chaperone proteins in the endoplasmic reticulum of the plasma cell [22]. Because an intact CH2 domain is required for complement activation [23], it is not surprising that so many of our cases (90%) had tissue activation of complement on the glomerular paraprotein deposits, accompanied by hypocomplementemia in four. Sequencing of the paraproteins would be required to determine if there are unique mutations or substitutions in the variable region that characterize this entity, as has been determined for some type 1 IgGκ cryoglobulins and a case of MPGN with deposits of monoclonal lambda light chain dimers [9, 24]. Such amino acid substitutions of the variable regions of either the heavy or light chains can create additional positive charges or increase hydrophobicity, thereby altering protein conformation, aggregability, and/or tissue-binding properties.

The pathomechanisms mediating this form of renal disease associated with monoclonal gammopathy are unknown. It is unlikely that the paraprotein is deposited nonspecifically in glomeruli that have been damaged by other mechanisms, because no patient had evidence of underlying autoimmune, infectious, or other systemic disease that might provide a source of chronic antigenic stimulation [25]. It is also unlikely that this entity is mediated by the formation of antigen-antibody complexes following an antigen-driven immune response, as typifies most forms of immune complex-mediated glomerulonephritis [26]. The characteristic feature of immune complex-mediated glomerulonephritis is the polyclonal nature of the immune deposits, which stain for both kappa and lambda. Strong intensity for a single light chain, with complete negativity for the other, is not generally observed in immune complex–mediated glomerulonephritis, with the exception of rare cases of IgA nephropathy with unusually strong lambda dominance reflecting the predominance of IgAλ in the circulation [7]. Normal circulating IgG, on the other hand, has a kappa:lambda ratio of approximately 2:1 [28], which explains the similar intensity of kappa and lambda or the slight kappa predominance observed in most cases of glomerulonephritis due to IgG-containing immune complexes (such as MPGN, postinfectious glomerulonephritis, and lupus nephritis) [29]. We favor that the monoclonal IgG is deposited in the form of a free, noncomplexed immunoglobulin, which has the ability to aggregate to form definable electron dense deposits.

Morphologically, the glomerular lesions most closely resemble those of type 1 cryoglobulinemia, where a pattern of diffuse proliferative glomerulonephritis or MPGN is typically seen and may be accompanied by membranous and/or exudative features. Moreover, three patients had some pathologic features potentially related to cryoglobulinemia, including arteriolar Congo red–negative IgGλ deposits with mild arteriolitis (patient 4), focal intracellular crystals within glomerular macrophages (patient 1), and glomerular deposits with focal lattice-like organization and periodicity of 15 nm (patient 3). The latter ultrastructural features resemble those seen in cryocrystalglobulinemic deposits [30, 31]. However, none of our patients had a detectable cryoglobulin in the serum, despite repeated testing. In addition, none of our patients had a circulating rheumatoid factor, a frequent surrogate marker for mixed cryoglobulins. Finally, the absence of any systemic signs or symptoms of cryoglobulinemia support this hypothesis. Nonetheless, we cannot completely exclude the possibility of type 1 cryoglobulinemia in view of the well-known detection problems by standard methods and the ability of cryoglobulin concentrations to vary over time or following treatment. Precedents for monoclonal immunoglobulins to precipitate as granular electron-dense deposits mimicking immune complex glomerulonephritis can also be found in rare cases of monoclonal IgA-induced glomerulonephritis and cases of noncryoglobulinemic IgM deposition in patients with Waldenstrom's macroglobulinemia and glomerulonephritis [32, 33].

Monoclonal paraproteins usually induce a single pattern of renal injury, although dual patterns have been reported, including amyloid and LCDD [34], myeloma cast nephropathy and LCDD [2], amyloid and fibrillary glomerulonephritis [5], amyloid and microtubular deposits [4], and myeloma cast nephropathy and Fanconi syndrome [12]. Case 3, which has been reported previously, is an additional example of such an overlap: amyloid deposits of AL lambda type were distributed in vessel walls, whereas monoclonal IgGλ deposits with focal lattice-like substructure were present in glomeruli and were responsible for the patient's nephrotic syndrome [35]. This combination of patterns could be secondary to the emergence of a subclone that produces a monoclonal protein with different physicochemical properties or to local factors that influence fibrillogenesis and crystallization. Patient 1 had crystalloid inclusions within macrophages infiltrating the

glomerulus, resembling the changes reported in the entity "crystal-storing histiocytosis" [36]. Thus, this case had overlapping features between glomerulonephritis with nonorganized deposits and crystal-storing histiocytosis involving glomeruli.

CONCLUSION

Glomerulonephritis associated with monoclonal IgG deposition should be added to the expanding spectrum of renal diseases associated with monoclonal gammopathy. Diagnostic criteria include (*1*) the presence of glomerular monoclonal IgG deposits restricted to a single IgG subclass and a single light chain isotype, associated with endocapillary proliferative, membranoproliferative, or membranous features; (*2*) the presence of granular ("immune complex type") deposits by electron microscopy; and (*3*) the absence of clinical and laboratory evidence of cryoglobulinemia. This entity, which is eight-fold rarer than AL amyloidosis and approximately twice as rare as Randall type monoclonal immunoglobulin deposition disease, has received recent attention in the literature as non-Randall type monoclonal immunoglobulin deposition disease [8] and may pose diagnostic challenges in renal biopsy interpretation. Proper recognition of this novel form of glomerulonephritis requires, above all, careful immunofluorescence analysis. We recommend that cases with suspected monoclonal IgG deposition based on light chain isotype restriction be confirmed by immunostaining for the gamma heavy chain subclasses. Longer follow-up of this rare condition is needed to determine its implications for possible development of myeloma or other hematologic malignancy.

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