Paraneoplastic glomerulopathies: New insights into an old entity

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CASE PRESENTATIONS

Patient 1. A 49-year-old white man was referred to the Renal Division at Hôpital Tenon for investigation of nephrotic syndrome in the setting of bronchogenic carcinoma. Past medical history was unremarkable, except for two urinary tract infections; an intravenous pyelogram performed six months earlier had been normal. Three months before admission, anemia had been discovered together with an inflammatory syndrome. The patient had recently lost 6 kg. He also complained of cough of recent onset, although he had a 25-pack-year history of cigarette smoking. A chest radiograph revealed a dense opacity of the right lung apex. A CT scan showed that this mass was located in the apico-dorsal segment of the right upper lobe and was associated with enlarged lymph nodes and a pleural reaction. Bronchoscopy disclosed a necrotic tumor in the posterior and apical apertures of the right upper bronchus. Bronchial biopsies established a diagnosis of epidermoid bronchogenic carcinoma.

On admission, the patient looked tired and pale. His blood pressure was 120/80 mm Hg. Physical examination was normal, showing neither edema nor signs of tumor dissemination. Laboratory tests showed: hemoglobin, 12.4 g/dl; erythrocyte sedimentation rate, 86 mm/hr; total protein, 5.6 g/dl (albumin, 42%; alpha-1, 5%; alpha-2, 18%; beta, 16%; gamma, 19%); serum creatinine, 0.7 mg/dl; sodium, 135 mEq/liter; potassium, 4.2 mEq/liter; chloride, 96 mEq/liter; bicarbonate, 26 mEq/liter; and glucose, 106 mg/dl. Liver function tests were normal. A 24-hour urine collection contained 10 g protein. The urinary sediment showed 100,000 red blood cells/ml. Immunologic tests were negative, except for the presence of antinuclear antibodies (1:1000) but without anti-DNA antibodies. Ultrasonography revealed no abdominal abnormality and two normal-sized kidneys.

A renal biopsy was performed. Light microscopic examination (Fig. 1A) showed only hypertrophy of some podocytes. The capillary walls had a nearly normal appearance. Immunofluorescent examination revealed, however, typical subepithelial deposits brightly stained with anti-\(\gamma\), anti-\(\kappa\), and anti-\(\lambda\) antibodies. Droplets of polyclonal IgG and IgA also were seen in the cytoplasm of proximal tubules. Electron microscopy confirmed the presence of small, granular, electron-dense deposits on the outer aspect of the glomerular capillary basement membrane.

One week after biopsy, the patient was randomized after informed consent into the chemotherapy arm of a French protocol for the treatment of bronchogenic carcinoma. He received a single course of chemotherapy without corticosteroid (mitomycin, 6 mg/m² at day one; cisplatin, 30 mg; and ifosfamide, 1.5 mg/m² from day one to day three), followed one month later by surgery. Pre-operative staging showed a 50% reduction of the tumor mass but the persistence of high urinary protein excretion (7 g/day). Thoracotomy revealed a 7 cm in diameter neoplastic mass without signs of lymph node invasion and metastasis (stage T2, N0, M0). The patient then received three additional courses of the same chemotherapy regimen at one-month intervals.

A 24-hour urine collection contained 7 g protein eight days after total excision of the carcinoma, but proteinuria totally disappeared within two months. It did not recur when the patient presented five months after surgery with a mediastinal lymph node relapse, which was controlled by cobalt therapy. Three years after surgery, the patient is doing well, without either proteinuria or other manifestation of tumor recurrence.

Patient 2. A 59-year-old white man was referred to the Renal Division for investigation of a nephropathy associated with chronic lymphocytic leukemia (CLL). He had a 13-year history of cold-induced swelling of his hands and face with urticarial rash, which was highly sensitive to anti-histamine drugs.

Four years earlier, he had been referred to the Renal Division of Saint-Quentin General Hospital (Saint-Quentin, France) for edema of the legs. Physical examination at that time disclosed high blood pressure (190/110 mm Hg) and numerous small,
Fig. 1. Patient 1. (A) Light microscopy. Note discrete thickening of the glomerular capillary walls and mild podocyte hypertrophy (Masson trichrome; original magnification × 312). (B) Immunofluorescence with anti-γ antibody. Note typical subepithelial deposits (original magnification × 312).
A 58-year-old white man was referred to the Renal Division of Chartres Hospital (Chartres, France) for evaluation of edema. His medical record mentioned the detection of hematuria a few years earlier during a routine checkup and the recent onset of hypertension.

Clinical examination revealed a blood pressure of 170/100 mm Hg and edema of the legs. Laboratory tests showed a hemoglobin of 12.7 g/dl, a white blood cell count of 6.3 × 10^6/ml, and a platelet count of 290 × 10^6/ml. Total serum protein was 3.2 g/dl; serum creatinine was 1.2 mg/dl; and glycemia was in the normal range. Proteinuria was only 1.0 g/day. Liver function tests were normal. Because of marked hypoalbuminemia (2.3 g/dl), tests for protein-losing enteropathy and malabsorption were performed. All were negative, as was the search for amyloid deposits in gastrointestinal biopsies. Hematuria was present; there were 40,000 to 200,000 cells/ml. Serum electrophoresis showed hypogammaglobulinemia (IgG, 0.23 g/dl; IgA, 0.19 g/dl; IgM, 0.035 g/dl), and immunoelectrophoresis disclosed a monoclonal IgG in the serum and free light chains in the urine. The C3 and C4 complement levels were in the normal range. Searches for cryoglobulinemia were fruitless. A bone marrow aspirate contained 14% dystrophic plasma cells, consistent with multiple myeloma. Skeletal radiographs did not reveal osteolytic lesions.

A renal biopsy was performed. Light microscopic examination showed nodular glomerulosclerosis with a marked increase in mesangial matrix and irregular thickening of glomerular basement membranes (Fig. 3A). Mesangial nodules were stained with periodic acid Schiff. Only mild, focal thickening of tubular basement membranes was present. No evidence of amyloid was seen. Electron microscopy disclosed an expanded mesangial matrix with deposition of finely granular, electron-dense material within mesangial nodules. Glomerular basement membranes were irregularly thickened, due to a continuous band of granular, electron-dense material located in the lamina rara interna and/or in the lamina densa; this thickening often resulted in dense transformation of the whole basement membrane (Fig. 3B). By immunofluorescence, mesangial nodules and glomerular basement membranes were heavily stained with the anti-γ heavy chain conjugate (Fig. 4), but no staining was observed with the anti-κ or the anti-λ polyclonal and monoclonal antibodies. In addition, a faint staining of some tubular and vascular structures was visible with the anti-γ heavy-chain antibody. Furthermore, by using monoclonal antibodies specific for the γ heavy-chain constant domains, we found that the deposited heavy chain belonged to the γ1 subclass and lacked the C H1 domain (Fig. 4). The heavy chain in the circulating monoclonal IgG was also a C H1-deleted γ1 chain. Bone marrow studies (J.C. Brouet, Hôpital Saint-Louis, Paris) were consistent with the synthesis of a short γ heavy chain and normal-sized λ chains, which partly assembled covalently as half immunoglobulin molecules (composed of one λ and one short γ chain). A diagnosis of myeloma-induced heavy chain deposition disease was made.

The patient was subsequently begun on a chemotherapy regimen including vincristine, melphalan, cyclophosphamide, and prednisone, administered on a monthly basis for one year. During that time, his proteinuria disappeared, serum albumin returned to normal, and renal function remained stable. A
Fig. 2. Patient 2. (A) Light microscopy. Atypical membranous glomerulonephritis: in addition to the irregular aspect of the capillary walls, note segmental mesangial hypertrophy and cellular proliferation (silver stain; original magnification × 312). (B, C) Immunofluorescence microscopy. Diffuse granular deposits along the capillary walls with predominant subepithelial location. Staining was exclusive for IgG (B) and kappa light chain (C, next page). Original magnification × 312. (D) Electron micrograph of a glomerular capillary. Note subepithelial deposits of fibrillar material cut at various angles. Uranyl acetate and lead citrate (original magnification × 12,000. Reproduced from [46]).
Fig. 2. Continued.
Fig. 3. **Patient 3.** (A) *Light microscopy.* Nodular glomerulosclerosis. Note moderate mesangial hypercellularity, scarce double-contour aspects, and normal appearance of most tubular basement membranes. PAS stain (original magnification × 312). (B) *Electron micrograph of a glomerular capillary.* Note diffuse, finely granular, electron-dense deposits along the glomerular basement membrane with effacement of epithelial cell foot processes (uranyl acetate and lead citrate; original magnification × 12,000).
second renal biopsy showed significant improvement of the renal lesions. The patient’s treatment was then shifted to interferon α (9 × 10⁶ units/week).

After more than five years of follow up, he has no evidence of hematologic or renal disease. Immunoelectrophoresis did not disclose any monoclonal component. Bone marrow smears showed 2% plasma cells with a normal appearance. Serum creatinine was 0.8 mg/dl; serum albumin, 3.8 g/dl; 24-hour protein excretion less than 130 mg; and the urinary sediment was unaltered.

DISCUSSION

DR. PIERRE M. RONCO (Chief, Division of Nephrology and INSERM Unit 489, Hôpital Tenon, Paris, France): The term paraneoplastic syndrome refers to clinical manifestations that are not directly related to tumor burden, invasion, or metastasis, but are caused by the secretion of tumor cell products such as hormones, growth factors, cytokines, and tumor antigens. These three case reports, all different forms of paraneoplastic glomerulopathy, exemplify the heterogeneity of this disease. Diverse glomerular lesions occur in a variety of neoplasms; I will discuss several different pathophysiologic links between the glomerulopathy and the cancer. The order of presentation of the cases reflects our increasing level of pathophysiologic knowledge: whereas the pathophysiology of solid-tumor-associated glomerulopathies remains obscure, a molecular link, and even specific molecular abnormalities, can be demonstrated in lymphoplasmaic disorders.

The concept of paraneoplastic glomerulopathy was introduced in 1922 by Galloway [1]. In 1939, Cornig in Paris reported the first case of nephrotic syndrome and Hodgkin’s disease in his M.D. thesis. The first convincing clinicopathologic study was published in 1966 by Lee et al [2]. Of their 101 adult patients who presented with the nephrotic syndrome in a 10-year period, 11 (11%) were found to have carcinoma; this percentage represented 10 times the age-matched actuarial rate. Renal disease antedated the diagnosis of cancer in two-thirds of the study population. Of the 10 nephrotic patients with cancer in whom renal tissue was available, 8 had membranous glomerulonephritis (MGN). In 1977, Eagen and Lewis collected 171 cases of nephrotic syndrome associated with cancers including carcinoma, Hodgkin’s disease, non-Hodgkin’s lymphoma, leukemia, and plasma cell dyscrasia [3]. These studies highlighted the high prevalence of MGN (34%) and minimal change disease (MCD, 24%); the former was observed in 68% of the patients with a carcinoma, the latter in 50% of those with Hodgkin’s disease. Other types of glomerular lesions were described in this series and in more recent reports, including IgA nephropathy and Henoch-Schönlein pur-
Table 1. Renal complications of neoplasia (excluding paraneoplastic glomerulopathies)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical (direct)</td>
<td>Infiltration of renal parenchyma</td>
</tr>
<tr>
<td>Obstructive uropathy (retroperitoneal fibrosis)</td>
<td></td>
</tr>
<tr>
<td>Compression of renal artery or vein</td>
<td></td>
</tr>
<tr>
<td>Metabolic (indirect)</td>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td></td>
<td>Myeloma cast nephropathy</td>
</tr>
<tr>
<td></td>
<td>Electrolyte disturbances</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation and thrombotic microangiopathy</td>
</tr>
<tr>
<td>Treatment-induced</td>
<td>Tumor lysis syndrome</td>
</tr>
<tr>
<td></td>
<td>Lithiasis and uric nephropathy</td>
</tr>
<tr>
<td></td>
<td>Radiation nephropathy</td>
</tr>
<tr>
<td>Drug-induced tubulointerstitial disease (cisplatin, antibiotics)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombotic microangiopathy and mesangiolyis</td>
</tr>
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</table>

pura, and membranoproliferative and crescentic glomerulonephritis.

The prevalence of renal involvement in cancer patients has been analyzed in autopsy and clinical series. In the former, mesangial and subendothelial immunoglobulin (Ig) deposits were observed in 11 of 20 patients (55%) by Pascal and associates [4] and in 22 of 129 patients (17%) by Beaufils and colleagues [5]. I should stress, however, that glomerular lesions were absent or mild, limited to mesangial hypertrophy, and no epimembranous deposits were noted.

In two clinical series, the prevalence of renal involvement was low [6, 7]. Urinary protein excretion greater than 100 mg/liter and hematuria were detected in 10% and 7%, respectively, of 600 patients with bronchial carcinoma [6]. In another study [7], proteinuria greater than 0.1 g/liter was more common in patients with malignancies (174/504, 34%) than in control patients (39/529, 7%). Median urinary protein concentrations were 0.14 (0.07 to 0.29) g/liter in the former, and 0.07 (0.05 to 0.12) g/liter in the latter. However, the rates of renal manifestations in these studies overestimate the actual prevalence of paraneoplastic glomerulopathies for at least three reasons. First, the threshold of proteinuria selected by the authors was quite low, within the range of physiologic proteinuria. Second, hematuria was detected by qualitative dipstick tests only, without quantitation of the urinary sediment. Third, paraneoplastic glomerulopathies are not the only cause of urinary abnormalities in cancer patients (Table 1).

Conversely, the prevalence of cancer in patients with glomerulopathies is easier to establish (Table 2). Cancer occurs in 11% to 13% of patients with the nephrotic syndrome [2, 8]. Depending on the age of the patients and the type of glomerular lesions, cancer rates can reach as high as 22% in patients over the age of 60 presenting with MGN [8].

Following the order of case presentations, I will analyze first paraneoplastic glomerulopathies associated with carcinomas, then those induced by malignant hemopathies. The paraneoplastic origin of each glomerulopathy will be discussed according to clinical (mainly temporal) criteria and presumed pathophysiologic links connecting the cancer and the renal disease.

Carcinoma-associated paraneoplastic glomerulopathies

Table 3 lists the distribution of carcinomas in three representative series of carcinoma-associated paraneoplastic glomerulopathies [3, 18, 19]. The most frequent glomerulopathy by far is MGN. Associated carcinomas mostly occur in the lung and gastrointestinal tract. Although this preponderance might be related to the overall frequency with which these neoplasms arise, other common carcinomas, such as cancers of the breast and uterus, have only rarely been associated with specific glomerulopathies.

Membranous glomerulonephritis. It is a rare disease (annual incidence of 2.8 per 100,000 over the age of 60) compared with cancer (annual incidence > 1,000 per 100,000 in the same age period). Thus the finding of carcinoma in a patient with MGN forces us to question the link between the neoplasia and the glomerulopathy. Brueggemeyer and Ramirez calculated that the incidence of cancer in their population of 128 MGN patients was about 10 times higher than that observed in age-matched controls [20]. However, it is intriguing that subepithelial deposits were not found or were found very infrequently in autopsy series of cancer patients [4, 5; reviewed in 21].

Theoretically, the diagnosis of paraneoplastic glomerulopathy should rely on three strong criteria. First, a clinical and histologic remission occurs after complete surgical removal of the tumor or chemotherapy-induced complete remission of the disease. However, relatively few papers have reported remission of MGN following removal of a solid tumor [reviewed in 19]. This finding probably is due to the fact that the majority of carcinomas associated with MGN are surgically incurable at presentation. Moreover, in patients showing remission of the nephrotic syndrome, like Patient 1, histologic cure of the glomerulopathy is usually not verified by a renal biopsy for ethical reasons. Thus, one cannot exclude spontaneous remission of the nephrotic syndrome despite persistent subepithelial membranous deposits. I should stress that spontaneous remission of the nephrotic syndrome occurs in about 30% of patients presenting with idiopathic MGN within one year of follow up [22]. Second, a renal relapse accompanies recurrence of the neoplasia. In other words, proteinuria should directly correlate with tumor activity. In fact, the course of cancer and glomerulopathy can be dissociated, as in the first patient, who presented with a mediastinal lymph node...
Table 2. Prevalence of carcinomas and hemopathies in patients with glomerulopathies

<table>
<thead>
<tr>
<th>Syndrome or lesions</th>
<th>Number of patients</th>
<th>Prevalence of cancers (%)</th>
<th>Authors and years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome</td>
<td>101</td>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lee et al, 1966 [2]&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>76&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13</td>
<td>Zech et al, 1982 [8]</td>
</tr>
<tr>
<td>Membranous GN</td>
<td>82</td>
<td>6</td>
<td>Hopper, 1974 [9]</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>11</td>
<td>Row et al, 1975 [10]</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>5</td>
<td>Cahen et al, 1989 [12]</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>8</td>
<td>Burstein et al, 1993 [13]</td>
</tr>
<tr>
<td></td>
<td>31&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22</td>
<td>Zech et al, 1982 [8]</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Kingswood et al, 1984 [14]</td>
</tr>
<tr>
<td>Crescentsic GN</td>
<td>60</td>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Whitworth et al, 1976 [15]</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>9</td>
<td>Biava et al, 1984 [16]</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>184</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mustonen et al, 1984 [17]</td>
</tr>
<tr>
<td></td>
<td>26&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>All carcinomas
<sup>b</sup>Figure in brackets is reference number. Series are classified in chronologic order
<sup>c</sup>Patients over the age of 60 years

Table 3. Prevalence (%) of MGN and distribution (%) of carcinomas in three series of paraneoplastic glomerulopathies

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MGN, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69</td>
<td>68</td>
<td>44</td>
</tr>
<tr>
<td>Location of cancer</td>
<td>Location of cancer</td>
<td>Location of cancer</td>
<td>Location of cancer</td>
</tr>
<tr>
<td>Lung</td>
<td>49</td>
<td>43</td>
<td>50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>23</td>
<td>11</td>
<td>31&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Kidney</td>
<td>5</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Prostate</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Head and neck</td>
<td>7</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>*</sup>Location of cancer was available in 57 patients
<sup>a</sup>MGN: membranous glomerulonephritis
<sup>c</sup>One patient with both gastric carcinoma and lung metastasis

relapse in the absence of proteinuria. Third, a pathophysiologic link is established between the two diseases, including the detection of tumor antigens and antitumor antibodies within subepithelial immune deposits. Very few cases of MGN involving such immune complexes have been reported so far, however. Alpers and Cotran consequently have suggested that the association between malignancy and MGN has been overemphasized [21].

In patients in whom the diagnosis of paraneoplastic MGN is likely because of a clear temporal relationship between MGN and malignancy, the following features of the renal disease are notable. Compared to idiopathic forms, paraneoplastic MGNs are characterized by a marked male preponderance, mean age over 50, and a full-blown nephrotic syndrome always present. Of the patients with carcinoma and MGN, 40% to 45% clinically manifest the nephrotic syndrome prior to the diagnosis of their tumor. Simultaneous presentation occurs in about 40% of patients, and in the remaining 15% to 20%, renal disease becomes apparent following diagnosis of their tumor. In the majority of cases, the two processes manifest themselves within 12 months of each other [2, 3, 13, 18, 19]. The renal lesions are similar to those of idiopathic MGN, although several authors have noted the presence of numerous polymorphonuclear leukocytes in capillary loops, occasionally associated with intravascular hyaline thrombi in the absence of renal vein thrombosis [18].

Although it is generally agreed that a search for malignancy is warranted in all patients presenting with apparently idiopathic MGN, particularly those over the age of 50, the extent of the workup remains controversial. I believe that in addition to a thorough history of the patient with a search for personal and hereditary cancer risk factors, physical examination, and standard biologic tests, one should undertake basic routine cancer screening procedures, including a chest radiograph and a flexible colonoscopy. Further investigation, including flexible bronchoscopy or gastroscopy and CT scan, might be in order after this first-line evaluation. More important, these patients should be closely followed, as the malignancy could be occult and not detectable on initial routine screening.

Other carcinoma-associated glomerulopathies. Membranous glomerulonephritis is not the only paraneoplastic glomerulopathy (Table 2). Other varieties include
IgA nephropathy, crescentic glomerulonephritis, membranoproliferative glomerulonephritis (MPGN), and minimal-change disease (MCD). The IgA nephropathies deserve special comment. These lesions can be limited to the kidney or associated with Henoch-Schönlein purpura; one should suspect paraneoplastic IgA nephropathy if the patient has necrotic skin lesions in the absence of cryoglobulin. Of 26 patients aged 60 or older, 6 (23%) had an intercurrent malignancy in Mustonen et al’s series, whereas none of the 158 patients under age 60 had cancer (Table 2) [17]. Any IgA nephropathy in a patient over age 60 should prompt a search for a solid tumor, particularly in the respiratory tract, the buccal cavity, and the (naso)pharynx [17]. This association can, however, be fortuitious or be strengthened by alcoholism, which is a risk factor for both hepatopathy-induced IgA nephropathy and cancers of the upper respiratory tract. It is interesting that mesangial IgA deposits were found at autopsy in some individuals with gastrointestinal neoplasia without prior clinical evidence of renal disease [5]. Mustonen et al have suggested that invasion of mucosa by tumor cells raises the level of circulating IgA and possibly produces mesangial IgA deposits [17].

Several reports strongly suggest an association between rapidly progressive glomerulonephritis and carcinoma (and lymphoproliferative disorders); the prevalence of cancer was 7% to 9% in patients with a pathologic diagnosis of crescentic glomerulonephritis (Table 2) [15, 16]. In four of the seven patients reported by Biava et al, renal function improved following treatment of the underlying malignancy, which only consisted of surgery and/or irradiation in three of them [16]. In most instances, as in Biava’s patients, immunofluorescent examination shows fibrin deposits without immune reactants. In other cases, granular or linear immunoglobulin deposits are seen [15, 18, 19]. One patient with prostatic carcinoma had a crescentic glomerulonephritis with positive immunoperoxidase staining for both prostate-specific acid phosphatase and prostate-specific antigen, as well as immune deposits on electron microscopy in the glomerulus [23]. Of particular interest are four patients who presented with rapidly progressive glomerulonephritis, clinical evidence of vasculitis, and positive ANCA serology [24]. In all four patients, a carcinoma of either the respiratory or urinary tract was diagnosed soon after the finding of ANCAs, suggesting the paraneoplastic nature of the vasculitic process.

Membranoproliferative glomerulonephritis and minimal change disease also occur in patients with carcinoma, although these lesions are more typical of lymphoproliferative disorders; MPGN has been reported in patients with Wilms’ tumor and malignant melanoma [25]. Minimal change disease has been associated with a variety of carcinomas; although the nephrotic syndrome can remit completely after surgery [26], the number of observations is too small (<20) for one to conclude that a causal relationship exists between carcinoma and the renal disease [reviewed in 26, 27].

Carcinoma-associated amyloidosis deserves special discussion. Approximately 3% of renal cell carcinomas are associated with AA-type amyloidosis [reviewed in 28]; this systemic complication not only causes the nephrotic syndrome, but also liver and spleen involvement. Of all carcinomas associated with amyloidosis, 25% to 33% are renal cell carcinomas, yet this tumor accounts for only 2% to 3% of all carcinomas. The production of IL-6 by renal tumor cells could account for the fever and chronic inflammation frequently observed in these patients. Remission of the nephrotic syndrome can occur following nephrectomy. Renal amyloid deposits, however, seem more persistent than are liver and spleen deposits. More recently, cases of nonamyloid fibrillary glomerulopathy have been reported in patients with gastric adenocarcinoma or metastatic adenocarcinoma of the liver [reviewed in 29].

Pathophysiology of paraneoplastic glomerulopathies in carcinoma patients. Now I would like to discuss the pathogenesis of paraneoplastic glomerulopathies with granular immune deposits, mainly membranous glomerulopathy. Despite considerable efforts in many laboratories, including ours, identification of the human antigens implicated in primary (idiopathic) membranous glomerulopathies has been unsuccessful. Although megalin, the target antigen of Heymann’s nephritis—a faithful model of membranous nephropathy in the rat—is expressed on the brush border of the human proximal tubule, it is not detected on the human podocyte [30]. Megalin thus cannot serve as a target antigen for circulating antibodies in the human glomerulus as it can in the rat. But megalin might be an antigenic component of nephritogenic circulating immune complexes in renal-cancer-associated glomerulopathies. Ozawa and associates detected the renal brush-border lipoprotein antigen RTE (an antigenic mixture containing megalin) in glomerular deposits and anti-RTE antibodies in the serum from the same three patients [31], but their findings have not been confirmed yet.

Paraneoplastic glomerulopathies theoretically represent an attractive model for unraveling the pathogenesis of membranous glomerulonephritis because carcinomas are important sources of antigens that can prompt the production of specific antibodies. Both tumor antigens and the respective antibodies can associate in blood as immune complexes, which can subsequently deposit in tissues including the kidney; alternatively, tumor antigens with high affinity for basement membrane constituents can become planted into the glomerular capillary wall, and then participate in in-situ formation of immune complexes with free circulating antibodies. Numerous attempts have been made to identify tumor antigens or their specific antibodies in kidneys of cancer patients.
Table 4. Immunopathologic data in paraneoplastic glomerulopathies

<table>
<thead>
<tr>
<th>Location of cancer</th>
<th>Number of cases</th>
<th>Type of glomerulopathy</th>
<th>Deposited antigen</th>
<th>Reactivity of eluted Ig</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1</td>
<td>MGN</td>
<td>NI</td>
<td>Tumor antigen</td>
<td>[32]</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>MGN</td>
<td>CEA</td>
<td>NI</td>
<td>[33]</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>MGN</td>
<td>Tumor antigen</td>
<td>NI</td>
<td>[34]</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>MGN</td>
<td>NI</td>
<td>Normal lung tissue and tumor antigen</td>
<td>[35]</td>
</tr>
<tr>
<td>Stomach</td>
<td>3 (2 patients)</td>
<td>MGN</td>
<td>CEA</td>
<td>CEA (or CEA-like antigen)</td>
<td>[36]</td>
</tr>
<tr>
<td>Palate</td>
<td>1</td>
<td>MGN</td>
<td>CEA</td>
<td>NI</td>
<td>[37]</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td>MPGN</td>
<td>Tumor antigen</td>
<td>NIH</td>
<td>[25]</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
<td>Crescentic</td>
<td>PSAP/PSA</td>
<td>NI</td>
<td>[23]</td>
</tr>
<tr>
<td>Kidney (clear cell)</td>
<td>3</td>
<td>Deposits</td>
<td>RTE</td>
<td>Normal brush border, jejunal mucosa, tumor cell membranes</td>
<td>[31]</td>
</tr>
</tbody>
</table>

To my knowledge, tumor antigens or antibodies have been demonstrated in no more than 14 cases of paraneoplastic glomerulopathy (Table 4). Tumor antigens implicated in the formation of immune deposits have been the carcinoembryonic antigen, prostate-specific antigens, the renal antigen RTE, and other unidentified tumor products. Tumor antigens and their corresponding antibodies were associated in glomeruli in only seven patients [25, 31, 36, 38]. Four of these patients, however, had only mild glomerular lesions or none at all and no subepithelial deposits [31, 38].

The presence of tumor antigens and their corresponding antibodies in patients with paraneoplastic glomerulopathies does not mean, however, that they are involved in the initial pathogenetic process leading to the formation of immune deposits. Indeed, these components can become passively deposited because of increased glomerular permeability to proteins as a result of the initial insult.

Let me summarize. As Alpers and Cotran emphasized [21], although it is likely that cancer-associated membranous glomerulonephritis is immune-complex-mediated, the limitations of the immunologic studies performed, the high prevalence of circulating immune complexes, and the frequent deposition of non-pathogenetic glomerular immune reactants in patients with cancer have made it difficult to pinpoint tumor-associated antigens as the primary initiators of glomerular injury. To further analyze the implication of tumor antigens in paraneoplastic glomerulopathies, these antigens must be identified at the molecular level, and experimental models must be developed in animals immunized with a pure molecular species. Alternatively, it is possible that immune perturbations in cancer patients (that is, their producing antibodies to exogenous or endogenous antigens) make these individuals prone to developing immune-complex nephritis. Among the myriad possible endogenous antigens, the p53 protein is a potentially good candidate because different mutations of this genome-guarding molecule are known to occur depending on the location and type of cancer, the mutations resulting in production of anti-p53 antibodies [39].

Hemopathy-induced paraneoplastic glomerulopathies

The paraneoplastic nature of these renal lesions is easier to establish than are carcinoma-associated glomerulopathies because of the higher rate of complete remission of the malignant hemopathy, and because of the molecular link between the hemopathy and the glomerulopathy, often a monoclonal immunoglobulin, which provides a clear pathophysiologic explanation to the renal lesions observed. This distinction is well illustrated by Patients 2 and 3.

Hodgkin’s disease. The association between Hodgkin’s disease and glomerulopathy is probably the best known of the hemopathy-induced paraneoplastic glomerulopathies, although in two large series collecting 1,700 Hodgkin’s disease patients, only 0.4% of them had MCD and only 0.1% amyloidosis [40, 41]. In a more recent review, Moulin et al [42] have identified approximately 100 reports of Hodgkin’s-disease-associated glomerulopathy, mainly amyloidosis (37%) and MCD (42%) (Table 5). It must be noted, however, that most case reports of amyloidosis were published before 1970 and occurred late in the course of the disease. The markedly decreased incidence of amyloidosis in Hodgkin’s disease is most likely attributable to modern treatment protocols, which induce a rapid remission of the hemopathy. Franklin et al identified the type of amyloid deposit as AA [44]. We can assume that most, if not all, cases of amyloidosis previously reported were of the AA type because they occurred in late, inflammatory stages of the disease in the absence of an M-component.
At present, the most frequent glomerulopathy is MCD. In MCD, the nephrotic syndrome usually appears early, revealing the disease in about one-half the cases and sometimes even preceding it by several months; it rapidly disappears after effective treatment of Hodgkin’s disease, even if corticosteroids are not used; and it usually relapses simultaneously with the hemopathy, generally remaining highly responsive to specific treatment for the cancer. Renal manifestations also can occur in patients with hematologic relapse even if these manifestations were initially absent. Followup of Hodgkin’s disease therefore should include evaluation for proteinuria. No particular subgroup of Hodgkin’s disease patients, with regard to age, gender, or stage of the disease, appears to be more likely to develop MCD. However, MCD seems to be more frequent in “mixed cellularity” forms of Hodgkin’s disease [45].

Other glomerulopathies have been described in association with Hodgkin’s disease, albeit with lower frequency (Table 5). Six patients developed extracapillary glomerulonephritis with anti-glomerular-basement-membrane antibodies [reviewed in 42]. The pathogenesis of this association remains obscure but could involve the release and presentation of basement membrane nephritogenic epitopes or an abnormal immune response induced by Hodgkin’s disease.

Most studies devoted to the pathophysiology of glomerular lesions in Hodgkin’s disease have focused on MCD. They support the hypothesis that an alteration in T-lymphocyte function responsible for abnormal lymphokine production increases vascular permeability and leads to the nephrotic syndrome. The putative hyperpermeability factor of lymphocytic origin remains unidentified.

**Chronic lymphocytic leukemia (CLL) and related B-cell lymphomas.** Studies on glomerulopathies in these diseases have been greatly facilitated by the development of sensitive techniques for the characterization of circulating, urinary, and membrane immunoglobulin, and by immunohistochemical and ultrastructural studies of renal biopsy. Contrary to glomerular lesions observed in plasma cell dyscrasias, which are well identified and usually reported as series, those occurring in CLL have long been reported only as isolated cases. We published in 1992 the first series of 13 cases [46]; I have further reviewed 32 published observations for this Forum, thus establishing the relative prevalence of the various glomerular lesions (Table 5). In CLL and related low-grade B-cell lymphomas, MPGN and MGN are the most frequent glomerulopathies; extracapillary glomerulonephritis is rare by comparison with non-Hodgkin’s lymphomas.

The CLL-associated glomerulopathies generally fulfill the three criteria required for the diagnosis of paraneoplastic syndromes. First, they often reveal CLL and, as in Patient 2, the diagnosis of both diseases is made simultaneously in about 50% of patients. Nephrotic syndrome is present in 85% of patients and is associated with renal failure in 33%. Second, these glomerulopathies are highly sensitive to the chemotherapy used to control CLL. It is remarkable that of the nine successfully treated patients (for their hematologic disease) in our series, seven had full remission of their nephrotic syndrome, and renal function improved in seven, remaining stable in the two other patients. In five of the nine patients, these results were obtained with chlorambucil alone, a drug ordinarily not effective in idiopathic MPGN and MGN. This finding strongly suggests that improvement of the glomerulopathy was mainly due to control of the hematologic disease. Third, a dysproteinemia was detected in about one-half of the patients in whom it was sought. This alteration consisted of a cryoglobulin in nine

### Table 5. Glomerular diseases associated with Hodgkin’s disease, B-chronic lymphocytic leukemia (B-CLL), and non-Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Glomerular lesions</th>
<th>Hodgkin’s disease</th>
<th>B-CLL and low-grade B-lymphoma</th>
<th>Non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis</td>
<td>39 (37%)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MCD</td>
<td>45 (42%)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>FSG</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>MGN</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>MPGN</td>
<td>2</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>ExGN</td>
<td>6</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Other PGN</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>IgA GN</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MIDD</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Immunotactoid GN</td>
<td>0</td>
<td>4 (3)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

* Abbreviations are: MCD, minimal change disease; FGS, focal segmental glomerulosclerosis; MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; ExGN, extracapillary glomerulonephritis; PGN, proliferative glomerulonephritis; MIDD, monoclonal immunoglobulin deposition disease
* [3, 21, 40–43]
* [3, 21, 42, 46–48]
* [3, 21, 42, 43, 49]

<Figure in parentheses refers to number of cases classified as membranous glomerulonephritis and immunotactoid glomerulopathy>
From a pathophysiologic point of view, patients who have CLL with renal involvement illustrate the heterogeneity of paraneoplastic glomerulopathies and underline the necessity for sophisticated immunopathologic analyses to dissect the mechanisms at play. Schematically, patients can be divided into three groups. The first group includes patients with MPGN caused by cryoglobulinemia, mostly type II. The existence of type-I or type-II cryoglobulinemia is not surprising in a lymphoproliferative disorder such as CLL, in which the B-lymphocyte clone can be secretory. Cryoglobulins can be considered immune complexes in which the antigen is a polyclonal immunoglobulin (type-II or type-III cryoglobulin) or remains of undetermined nature (type-I cryoglobulin). In the case of type-II and type-III cryoglobulins, the polyclonal immunoglobulin itself is endowed with antibody activity that is most often not identified. Gilboa et al made an interesting observation in two patients with CLL associated with MPGN, hypocomplementemia, and type-I cryoglobulinemia composed of an IgGκ M-component [50]. Their finding that immunoglobulin eluted from both the glomeruli and the serum cryoglobulin bound in vitro to patients’ glomeruli but not to normal glomeruli suggested that the monoclonal IgGκ was directed to non-glomerular antigens. The latter might be lymphocyte antigens as suggested by Day and colleagues [51] or non-lymphocyte antigens, including viral antigens. On the other hand, because of cryoglobulin’s ability to precipitate in vessels under certain circumstances, we also should suspect a direct pathogenetic role for it, irrespective of cryoglobulin composition.

The second group, to which Patient 2 belongs, is characterized by monoclonal immunoglobulin deposits in the absence of cryoglobulinemia, with or without a circulating M-component. Some of these patients present with features typical of monoclonal immunoglobulin-deposition disease (MIDD) with nodular glomerulosclerosis stained with the anti-κ or anti-λ light-chain antibody [47]. Others have an atypical form of MGN, usually with thick, fibrillar deposits seen on electron microscopy [52, 53]. The microtubular aspect of the deposits and the absence of tubular basement membrane staining with anti-light-chain antibodies distinguish these cases from MIDD, in which the deposits display a granular pattern; instead these alterations recall the ultrastructural lesions described in immunotactoid glomerulopathy. Korbet et al reported one patient with immunotactoid glomerulopathy and CLL [54]. Touchard and associates’ finding of organized microtubular structures in the cytoplasm of circulating lymphocytes suggested yet undefined physicochemical anomalies of the M-component that lead to its rapid deposition [52]. They proposed the term “glomerulonephritis with organized microtubular monoclonal immunoglobulin deposition” (GOMMID) for this novel CLL-associated paraneoplastic glomerulopathy. Additional cases have been reported in non-Hodgkin’s low-grade lymphomas. Finally, in a third group of patients presenting with various glomerular lesions (including FSG, crescentic GN, and advanced fibrotic lesions) and neither cryoglobulin nor monotypic glomerular deposits, a clear-cut pathophysiologic link between CLL and the glomerulopathy could not be established [46].

Plasma cell dyscrasias. Various types of glomerular diseases occur in patients with plasma cell dyscrasias (PCD). These diseases can be classified into two categories by electron microscopy. The first, characterized by organized deposits, includes diseases with fibrillar deposits, mainly amyloid light-chain (AL) amyloidosis, and diseases with microtubule formation such as cryoglobulinemic glomerulonephritis. The second category, which mostly includes MIDD, is defined by non-organized deposits usually exhibiting a granular appearance. The most frequent glomerulopathy in PCD is AL amyloidosis, found in about 11% of myeloma patients at autopsy [55]. Amyloid light-chain amyloidosis fulfills the criteria of a truly paraneoplastic disease: it often reveals the PCD; the precursor of amyloid fibrils is the light chain, mostly λ, produced by the plasma cell clone; and regression of amyloid deposits can be observed when the secreting clone is eradicated, mainly by intensive chemotherapy with the support of syngeneic bone-marrow transplantation or blood stem-cell autografting [56]. I will not detail the characteristics of amyloidosis because it is a well-known entity [reviewed in 57, 58].

It has been known since the late 1950s that nonamyloidotic forms of glomerular disease resembling the lesion of diabetic glomerulosclerosis also could occur in multiple myeloma. The presence of monoclonal light chains in these lesions was recognized later by Randall et al, who published the first description of light-chain deposition disease (LCDD) [59]. The finding of both monoclonal heavy chains and light chains in the tissue deposits from some patients defined light- and heavy-chain deposition disease (LHCD). More recently, deposits containing monoclonal heavy chains only (HCDD), that is, in the absence of detectable light chains, were observed in patients with otherwise typical Randall’s disease [60]. In clinical and pathologic terms, LCDD, LHCD, and HCDD are basically similar and are therefore also referred to as monoclonal immunoglobulin deposition disease. They differ from amyloidosis by their lack of affinity for Congo red stain and by the lack of fibrillar organization of the deposits, which usually display a granular appearance on electron microscopy. An
Table 6. Prevalence of clinical manifestations and glomerular lesions in monoclonal immunoglobulin-deposition disease (MIDD)

<table>
<thead>
<tr>
<th>Type of MIDD</th>
<th>Number of patients</th>
<th>Male/Female ratio</th>
<th>Age, years (range)</th>
<th>Hypertension</th>
<th>Renal failure*</th>
<th>Nephrotic syndrome</th>
<th>Hematuria</th>
<th>Nodular glomerulosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCDD and LHCDD*</td>
<td>64</td>
<td>1.6</td>
<td>54 (31–77)</td>
<td>55%</td>
<td>89%</td>
<td>44%</td>
<td>44%</td>
<td>61%</td>
</tr>
<tr>
<td>HCDD*</td>
<td>12</td>
<td>2.0</td>
<td>57 (35–79)</td>
<td>82%</td>
<td>83%</td>
<td>58%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* LCDD and LHCDD data from Refs. 63–66; HCDD data reviewed in Ref. 58
b Serum creatinine > 130 μmol/liter

extensive description of LCDD appears in several reviews [59, 61, 62]. Clinical manifestations are summarized in Table 6 from the four largest series yet published [63–66]. Table 6 also shows the clinical data in the 12 known cases of HCDD [reviewed in 58]. The higher prevalence of hypertension, nephrotic syndrome, and hematuria might be accounted for by the greater severity of renal lesions; nodular glomerulosclerosis was observed in all patients with HCDD.

Monoclonal immunoglobulin-deposition disease is a paraneoplastic systemic disease that affects basement membranes in most tissues, although the distribution can be more restricted in HCDD. The most common underlying disease is myeloma, which accounts for 40% to 50% of LCDD and 25% of HCDD. Autopsy revealed MIDD in about 5% of myeloma patients [55]. Other malignancies occasionally involved are CLL and Waldenström’s macroglobulinemia. Like AL amyloidosis, MIDD also can occur in the absence of a detectable malignant process, even after prolonged follow up (longer than 10 years). This finding illustrates that the same disease can be induced by a light chain produced by either a malignant or a benign plasma-cell clone; thus paraneoplastic-like glomerulopathies can occur with benign proliferation. At least two retrospective studies have shown the potential renal benefits of chemotherapy [66, 67] although, as for amyloidosis, regression of light-chain deposits is rarely observed.

Monoclonal immunoglobulin-deposition disease provides a unique opportunity for analysis of the pathogenesis of some paraneoplastic glomerulopathies at the molecular level, because the nephritogenic molecule is a monoclonal immunoglobulin subunit. In LCDD, several characteristics of light chains might partially explain their pathogenicity [reviewed in 58]. Table 7 compares these characteristics with those of amyloidogenic light chains, because different physicochemical properties of these molecules are likely responsible for the granular (in MIDD) or fibrillar (in amyloidosis) aspect of the deposits [reviewed in 58].

Patient 3, who had myeloma-induced HCDD, shows that a detailed analysis of the serum and the renal biopsy with specific anti-constant domain antibodies can provide further insight into the pathogenesis of the disease.

In our patient as well as in the 6 others [68] in whom a structural analysis of the heavy chain was performed either by epitope mapping of the constant domains of the circulating or the deposited heavy chain or by sequence analysis [69], a deletion of the first constant domain C\textsubscript{H1} was observed. In the blood the deleted heavy chain was associated with light chains, mostly of the λ isotype, or circulated in small amounts as a free unassembled subunit. Since the retention of free heavy chains in the endoplasmic reticulum before their association with light chains requires binding of chaperone proteins to the C\textsubscript{H1} domain, we can deduce that the C\textsubscript{H1} deletion facilitates the secretion of free unassembled or partially assembled heavy chains that are rapidly cleared from the circulation by organ deposition. Although deletion of the C\textsubscript{H1} seems to be necessary for the development of HCDD, the deletion is not sufficient. Similar deletions indeed are found in heavy-chain disease, a lymphoproliferative disorder in which renal tissue deposition of the truncated heavy chains has not yet been documented, and in AH amyloidosis, in which deposits have a fibrillar organization [69]. These data suggest that the variable domain of the heavy chain (V\textsubscript{H}) is also required for tissue precipitation.

Although a monoclonal component usually represents the molecular link between the plasma cell proliferation and the glomerulopathy in PCD, there are puzzling exceptions characterized by the occurrence of severe glomerulonephritis in the absence of M-component depositi-
Conclusion

The best example is the glomerulopathy of POEMS syndrome, also called Crow-Fukase syndrome, a multisystemic disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes [70]. A variety of glomerular alterations have been described, including MPGN-like, microangiopathic, and mesangiolytic lesions, but without deposition of the M-component [71]. In the forms with a localized plasmacytoma, removal of the tumor induced dramatic improvement of the clinical manifestations. The role of growth factors, including interleukin-6 and vEGF [72, 73], has been proposed to explain endothelial proliferation and associated vascular lesions. POEMS-related glomerulopathies share common features with Castleman’s disease, a lymphoproliferative and vascular disorder that is sometimes associated with POEMS syndrome. The finding of human herpesvirus-8 (HHV-8) in about 40% of non-HIV patients with Castleman’s disease [74] and the angiogenesis-activating properties of HHV-8, the Kaposi’s sarcoma-associated herpesvirus (KSHV) [75], suggest that HHV-8/KSHV is implicated in the pathophysiology of vascular lesions.

Non-Hodgkin’s lymphoma (NHL). Patients with NHL manifest a great variety of glomerular lesions (Table 5) [49]. Contrary to the observations made in Hodgkin’s disease, MCD is rare in NHL; the most frequent glomerulopathies are MPGN and crescentic glomerulonephritis. Because of the diversity of renal lesions, an important question is whether the association between NHL and glomerulonephritis is coincidental. As for CLL, a clear-cut relationship can be established in patients with cryoglobulinemic MPGN and in those with immunotactoid glomerulonephritis with monotypic immunoglobulin deposits.

QUESTIONS AND ANSWERS

Dr. John T. Harrington (Dean, Tufts University School of Medicine, Boston, Massachusetts): The common theme in all these patients is proteinuria secondary to increased glomerular permeability. Could you speculate on the lymphokines that might be involved? Second, have serum or cells from patients with Hodgkin’s disease and MCD been shown in experimental tissue systems to increase basement membrane permeability?

Dr. Ronco: The most appropriate neoplasia for discussing the role of lymphokines as permeability factors is a priori Hodgkin’s disease because proteinuria usually occurs in the absence of glomerular lesions and also because lymphokines have been involved in several manifestations of the disease. However, the view that Hodgkin and Reed-Sternberg cells, which both have been assigned to the B-cell compartment [76], increase glomerular permeability via the secretion of a single lymphokine is far too simplistic. First, Hodgkin and Reed-Sternberg cells usually make up less than 1% of the tumor cell mass, which is mainly composed of a polymorphic cellular infiltrate comprising T-cells, eosinophils, neutrophils, plasma cells, histiocytes, and fibroblasts in close vicinity to the malignant cells. Second, a great variety of lymphokines and growth factors (IL-1, IL-2, IL-4, IL-6, IL-7, IL-9, IL-12, TNF, lymphotoxin-α, INF-γ, GM-CSF, etc.) are produced both by infiltrating and tumor cells [76]. These cytokines can act locally to support growth of Hodgkin and Reed-Sternberg cells and systemically as immune or pro-inflammatory mediators. Sustained secretion of IL-1, IL-6, and TNF most likely accounts for increased liver production of SAA and the development of AA-type amyloidosis in the few patients with uncontrolled Hodgkin’s disease. In contrast, it is as yet impossible to tell which cell type and which lymphokine are responsible for MCD. It seems likely, however, that proteinuria is caused by infiltrating activated T-cells rather than by tumor cells.

With regard to your second question, one approach to the identification of the permeability factor produced in some patients with Hodgkin’s disease would involve testing the glomerular effects of pure or fractionated serum and cells (or cell supernatants) on basement membrane permeability. To my knowledge, only one report addressed this important question [77]. Glomerular permeability did not increase in any rats or mice injected or perfused with serum or cell-culture supernatants from a patient with Hodgkin’s disease and MCD. Moreover,
Dr. Maurice Laville: The term “paraneoplastic” means. Do you call myeloma cast nephropathy one year after removal of the tumor and that the patient is irrel- 

Dr. Ronco: I am not aware of any animal model for paraneoplastic glomerulopathies.

Dr. Harrington: Are there any good animal models for paraneoplastic glomerulopathies?

The development of such a model would require grafting of carcinoma cells from patients with paraneoplastic glomerulopathy to immunodeficient mice. However, animals can die before developing proteinuria. The lack of progress in the pathophysiology of MGN in humans seems to have discouraged research in the field of paraneoplastic MGN. It is much easier to inject mice with plasma cells producing a nephritogenic immunoglobulin. An animal model of MIDD has thus been established. It allowed identification of the role of amino acid substitutions in V-region sequences of the light chain.

Dr. Jean-Louis Preud’homme (Laboratoire d’Immunologie et d’Immunopathologie, CNRS ESA 6031, University Hospital, Poitiers, France): While there is virtually nothing to add to the very nice and thorough discussion by Dr. Ronco, I would like to make a comment. The term “paraneoplastic” appears to be both inappropriate and confusing. It lumps together completely unrelated processes, the rather poorly understood lesions observed in carcinomas and Hodgkin’s lymphoma, on the one hand, in which the renal disease is indeed paraneoplastic, and lesions directly linked to monoclonal immunoglobulins in immunoproliferative disorders, on the other hand. In the latter conditions, if the underlying hematologic condition is malignant, the renal lesion relates to an intrinsic and major function of the proliferating cells and the relationship is direct and not lateral or indirect, as “para” means. Do you call myeloma cast nephropathy paraneoplastic? More important, the overtly malignant or apparently benign condition of the hemopathy is irrelevant. Two-thirds of AL amyloidosis and one-third of LCDD patients have no malignant disease, and yet the visceral lesions are the same as those in patients with myeloma. The causes of the disease are molecular abnormalities of immunoglobulin chains that are unrelated to malignancy.

Dr. Ronco: I agree that the term “paraneoplastic” is ambiguous in some instances. As I specified in my discussion, this term refers to clinical manifestations that are not directly connected to tumor mass, compression, or metastasis and that regress when the tumor is cured. In my opinion, this definition not only fits with carcinoma- and Hodgkin’s disease-associated glomerulopathies, but also with glomerulopathies observed in immunoproliferative disorders. The fact that the molecular link, which usually is a monoclonal immunoglobulin, is known in the latter glomerulopathies does not rule out that they are paraneoplastic. Nor will this adjective become inappropriate when the putative lymphokine(s) involved in Hodgkin’s disease-associated MCD or the antigen released by tumor cells in carcinoma-associated MGN are identified. In this respect, one of the most characteristic paraneoplastic syndromes is Schwartz-Bartter syndrome, which occurs in small-cell lung carcinomas producing arginine vasopressin. I do admit, however, that the classification of myeloma cast nephropathy is difficult because this disease, caused by light-chain precipitation in distal tubule lumens, occurs almost exclusively in myeloma patients with high tumor burdens. Finally, I fully agree that renal manifestations in AL amyloidosis and LCDD patients mainly depend on abnormalities of immunoglobulin chains that are unrelated to malignancy. Thus the same renal disease can be observed in malignant and nonmalignant conditions provided they share the same molecular link.

Dr. Daniel Cordonnier (Service de Néphrologie, University Hospital, Grenoble, France): A key feature of carcinoma-associated glomerulopathy is the disappearance of proteinuria and other renal symptoms after removal of the tumor. You said that a second renal biopsy at the time of complete remission is usually not performed for ethical reasons. Are you aware of case reports demonstrating histologic remission of the renal disease?

Dr. Ronco: I know about one report of complete histologic remission of MGN after resection of an adenocarcinoma of the ascending colon. Kidney tissue was available seven years after remission of the nephrotic syndrome because a left nephroureterectomy was done after detection of a renal cell cancer. No evidence of MGN was found by light microscopy, immunofluorescence, and electron microscopy. I should stress, however, that remission of the nephrotic syndrome occurred about one year after removal of the tumor and that the patient received high-dose steroids for several months.

Dr. Maurice Laville (Département de Néphrologie, Hôpital Edouard-Herriot, Lyon, France): Both malignant and nonmalignant lymphoid tissue proliferations can be associated with paraneoplastic glomerulopathies. Do you think that the lymphoid tissue reaction to carcinoma rather than the release of tumor antigens is responsible for the development of proteinuria and glomerular lesions?

Dr. Ronco: Your suggestion is very interesting, indeed. Solid tumors often are associated with an intense inflammatory reaction that can evolve into granulomas, as in Hodgkin’s disease. Few cases of carcinoma complicated by MCD have been reported. Lymphokines produced by infiltrating lymphocytes and macrophages can increase glomerular permeability.
and cause MCD. They also can disturb immunologic pathways leading to the production of antibodies against tumor or self antigens and to the development of MGN.

**Dr. Gilbert Deray (Département de Néphologie, Hôpital de la Pitié-Salpêtrière, Paris, France):** It has been suggested that fetal antigens expressed in carcinoma cells are involved in the pathogenesis of paraneoplastic MGN. Could you speculate on this hypothesis?

**Dr. Ronco:** Carcinoembryogenic antigen (CEA) is a good example of an antigen, expressed during embryogenesis in digestive tissues, that can be re-expressed in adulthood in a variety of conditions including cancer, inflammatory intestinal diseases, liver diseases, chronic lung diseases, and heavy smoking. Indeed, CEA or CEA-like antigen has been detected in several cancer patients with MGN [33, 36, 37], but as I said, its presence in subepithelial deposits can result from increased permeability of the glomerular basement membrane to proteins, as shown for albumin in Heymann’s nephritis. It is not yet possible to implicate CEA or other tumor antigens in the pathogenesis of paraneoplastic MGN. To address this important issue, it would be necessary to set up an experimental model in mice or rats immunized with those antigens.

**Dr. Jean-Pierre Clauvel (Service d’Immuno-Hématologie, Hôpital Saint-Louis, Paris):** Your first patient presented with a mediastinal lymph node relapse without recurrence of the nephrotic syndrome. This interesting observation suggests that the tumor mass also can contribute to the pathogenesis of paraneoplastic syndromes. In my own experience with diffuse monoclonal proliferation of CD8 T-cells and neutropenia, removal of a large tumor—for instance, splenectomy—is often associated with a dramatic increase of the neutrophil polymorphonuclear cell count.

**Dr. Ronco:** Because our first patient also received three courses of chemotherapy after surgery, it is difficult to establish whether the absence of renal relapse was accounted for by chemotherapy or by the lower tumor mass of mediastinal lymph nodes. I agree that full-blown expression of paraneoplastic glomerulopathies can indirectly be linked to tumor burden in carcinoma patients.

**Dr. Philippe Lesavre (Département de Néphrologie, Hôpital Necker, Paris):** Laure-Hélène Noël in our group studied the isotype of the deposited IgG in idiopathic forms of MGN [83]. She found that the isotype was restricted to IgG1 and IgG4. This finding might indicate an auto-antibody nature of the deposited IgG. Are you aware of such a study in paraneoplastic forms of MGN?

**Dr. Ronco:** Unfortunately, I know of no study dealing with this important issue.

**Dr. Jérôme Rossert (Département de Néphrologie, Hôpital Tenon, Paris):** Paraneoplastic MGNs mostly occur during the evolution of lung carcinomas or of colonic carcinomas. Can you speculate on the mechanisms linking these carcinomas, and not others, to MGN? In particular, you suggested that anti-p53 antibodies play a role in the pathogenesis of paraneoplastic MGN. Are mutations in p53 occurring with a particularly high frequency during the evolution of lung and colonic carcinomas?

**Dr. Ronco:** Mutations in p53 are indeed more frequent in lung (60%) and pancreatic (44%) cancers than in any other (bladder, 34%; breast, 22%; in controls, the mutation rate is zero) [39]. Consequently, the percentage of patients with anti-p53 antibodies is the highest in patients with lung (24%) and pancreatic (19%) cancers (bladder, 17%; breast, 12% to 14%) [39].

**Dr. Jean-Daniel Sraer (Département de Néphrologie, Hôpital Tenon, Paris):** There is a high incidence of de-novo MGN in renal transplant recipients, as compared to the general population. Recipients of renal transplants also have an increased incidence of malignancy. What do we know about paraneoplastic GN in these patients?

**Dr. Ronco:** I am not aware of any case of carcinoma-associated glomerulopathy in patients who have received renal transplants.

**Dr. Vincent Esnault (Service de Néphrologie-Immunologie, University Hospital, Nantes, France):** I am puzzled by the complement drop in your second patient, who had organized microtubular monoclonal deposits, as well as in several patients with HCDD. How do you explain complement consumption in those patients?

**Dr. Ronco:** Patient 2 had a transient decrease in CH50 at the time of referral, but normal C3 and C4 fractions. Although Patient 3 with γ1-HCDD had normal complement levels, signs of complement consumption were found in three of four patients with γ1-HCDD, in all three patients with γ3-HCDD, and in none of the two patients with γ4-HCDD as yet reported [reviewed in 68]. The lack of complement activation in patients with γ4-HCDD is not surprising since γ4 does not activate complement. Two regions play a critical role in complement activation: the C1q2 that expresses the C1q binding site, and the hinge region that confers flexibility to the immunoglobulin molecule [84]. I should stress that deletion of the C1q1 was found in all seven patients in whom this anomaly was sought [68]. I am aware of two additional HCDD cases with a C1q1 deletion. This C1q1 deletion might increase accessibility of C1q to its binding site on the C1q2, and this in turn might initiate complement activation [85].

**Dr. Christian Combe (Service de Néphrologie, Hôpital Saint-André, Bordeaux, France):** As you mentioned in your presentation, mesangiotproliferative glomerulonephritis have been described in some patients with Castleman’s disease [86], which often is associated with Kaposi’s sarcoma-associated herpesvirus (KSHV/HHV-8) infection. Since high plasma levels of IL-6, a potent mediator of glomerular inflammation [87], have been reported in these patients [86], do you think that viral infection...
could contribute via IL-6 production to the pathogenesis of the glomerulonephritides associated with Castleman’s disease? Is there any evidence for the implication of other viruses in cancer-associated glomerulopathies?

Dr. Ronco: This question offers me the opportunity to discuss both the concept and the pathophysiology of paraneoplastic glomerulopathy in the setting of a rare, polymorphic disease that can evolve as a benign disorder or a malignancy. Castleman’s disease occurs in two forms: a localized, usually mediastinal lymphoid mass, and a systemic variant that involves multiple lymphoid regions and other organs. The former responds to local treatment, whereas multicentric Castleman’s disease has an aggressive clinical course and is frequently fatal. Lesions are classified histologically as the common hyaline-vascular type (80% to 90%) or the rarer plasma cell type (10% to 20%) [88]. Castleman’s disease is also referred to as angiofollicular lymph node hyperplasia, a term that points to vascular proliferation, a key feature of the disease. Most cases include systemic symptoms (fever, weight loss, asthenia) and signs of inflammatory activity, both being caused by the lymph node lesion; all symptoms and signs disappear after surgical excision or successful medical treatment of the mass.

Recent data indeed suggest that excessive IL-6 production by plasma cells and cells of the germinal centers play a role in the genesis of systemic and renal manifestations of Castleman’s disease [86]. Renal complications include AA-type amyloidosis, MPGN, thrombotic microangiopathy, and acute interstitial nephritis (Kazes I, unpublished data). Reversal of nephrotic syndrome due to AA-type amyloidosis [89] and resolution of MPGN [90] were observed after excision of a giant axillary lymph node and prednisolone and cyclophosphamide therapy, respectively. Relapse of Castleman’s disease occurred with increasing proteinuria [90]. Most likely, IL-6 is an important molecular link between the lymphoproliferative disorder and glomerular lesions because IL-6 increases SAA protein synthesis by hepatocytes [91] and increases mesangial cell proliferation and matrix production in vivo [87]. Castleman’s disease-associated glomerulopathies thus fulfill all the criteria for paraneoplastic glomerulopathies although the underlying hemopathy often is benign.

The detection of HHV-8/KSHV in 40% of HIV-negative patients with Castleman’s disease [74] and the demonstration of viral genes encoding vIL-6, Bcl-2, and cyclins [92] led to the suggestion that the virus could be implicated both in B-cell proliferation and in systemic and renal manifestations of Castleman’s disease. In addition, the tropism of HHV-8/KSHV for endothelial cells [93] and its angiogenic effects mediated by a G-protein-coupled receptor and vEGF secretion [74] might account for the development of vascular lesions that occur in association with MPGN or in the form of thrombotic microangiopathy.

With regard to your last question, the implication of other viruses in cancer-associated glomerulopathies is indeed plausible. Hepatitis-C virus infection is known to trigger B-lymphocyte proliferation that can evolve into lymphoma and be associated with cryoglobulinemic MPGN [94].

Dr. Clauvel: The detection of HHV-8 in malignant and nonmalignant hemopathies indeed represents a major breakthrough in the pathophysiology of these diseases. The finding of HHV-8 sequences in bone marrow dendritic cells of myeloma patients [95] is a debated issue, but it has been recently confirmed by several groups. Also, HHV-8 sequences have been found in bone marrow dendritic cells in AL amyloidosis (abstract, Blood 92:261a, 1998) and in POEMS syndrome (unpublished data).

Dr. Jean-Charles Piette (Service de Médecine Interne, Hôpital de la Pitié-Salpêtrière, Paris): We retrospectively looked for antibodies to HHV-8 in 13 patients with POEMS syndrome. Four of these patients also had Castleman’s disease. Anti-HHV-8 antibodies could be detected in only one of the 13 patients, who did not have Castleman’s disease (Papo T, unpublished data). We also found very high serum levels of vEGF in eight patients with POEMS syndrome; however, vEGF levels were similar in patients with (n = 4) and without (n = 4) renal involvement [96].

Dr. Clauvel: The lack of antibodies in some series of patients with Castleman’s disease does not exclude HHV-8 infection. In our own series, antibodies were detected in 90% of the patients. Such discrepant results could be explained by technical problems. Anti-HHV-8 antibodies also have been detected in myeloma patients [97]. The absence of these antibodies could be due to the small numbers of dendritic cells infected with HHV-8 and to the low copy number of virus in any individual cell [98].

Dr. Cordonnier: In your second patient with CLL-related glomerulopathy, subepithelial deposits had a fibrillar structure made of microtubules with a diameter of 22 nm. The size and structure are reminiscent of those of IgGk described in monoclonal cryoprecipitates by our group in 1979 [99]. I would suggest that the link between the few blood cells that showed cytoplasmic spots of γ and κ chains and the renal deposits could have been a transient cryoglobulin inducing complement consumption.

Dr. Ronco: Although the hypothesis of a transient cryoglobulinemia cannot be ruled out completely, the renal lesions were not suggestive of a cryoglobulinemic kidney mainly because there was no subendothelial deposit. In fact, the renal lesions were similar to those found in GOMMID [52].

Dr. Guy Touchard (Service de Néphrologie, University Hospital, Poitiers): Patient 2 is affected with the condition we have described as GOMMID in every as-
pect, including response to chemotherapy [52]. This entity was diagnosed in five of our six patients presenting with the nephrotic syndrome associated with CLL. The sixth patient also had organized microtubular immunoglobulin deposits, but these deposits were not monotypic, as they contained \( \gamma, \mu, \kappa, \) and \( \lambda \) chains. Also, GOMMID was found in one patient with a benign monoclonal gammopathy (MGUS) and in three patients without overt plasma cell dyscrasia. We could not detect the deposited M-component in the serum and the urine even by the sensitive Western blotting method in two of five patients with GOMMID and CLL and in two of four patients with GOMMID not linked with CLL.

**Dr. Preud’homme:** One may regret that in Patient 2, circulating M-components were not sought by Western blotting, which is more sensitive than immunofixation by several orders of magnitude. In addition, cytoplasmic immunochemistry and electron microscopic studies of the lymphocytes could have provided evidence of a direct relationship between CLL and renal deposits.

**Dr. Ronco:** Patient 2 was referred to us several years ago, before Western blotting was commonly used as a sensitive method for detecting M-components. We could not identify with certainty whether the cytoplasmic spots of \( \gamma \) and \( \kappa \) chains were localized in lymphocytes; neither could we detect organized deposits in lymphocytes by electron microscopy because of the small number of circulating lymphocytes during chemotherapy.

**Dr. Touchard:** Concerning the classification of granular (non-organized) monoclonal immunoglobulin deposits, it seems important to distinguish two types of deposits according to their localization: Randall-type granular deposits affecting glomerular and tubular basement membranes, and non-Randall-type granular deposits affecting the subepithelial and subendothelial spaces of glomerular capillary wall and often the mesangium but not the peritubular area. We recently studied a patient with type-III MPGN and granular non-Randall-type monoclonal \( \lambda \) light-chain dense deposits in mesangial, subepithelial, and intramembranous areas. The monoclonal \( \lambda \) light chain activated the alternative pathway of complement, probably by interacting directly with factor H as previously reported [100]. Certainly LCDD, HCDD, and LHCDD are the most frequent forms of MIDD, but there is still room for other variants of the disease.

**Dr. Ronco:** We have also encountered cases of MIDD with non-organized granular deposits restricted to the glomerulus. I agree that MIDD can be more heterogeneous than expected. Patients with MIDD should be classified according to the type of deposited M-component and to the precise location of the deposits.

**Dr. Rossert:** During the course of MIDD, there is deposition of a monoclonal component but also a striking accumulation of extracellular matrix. Could you speculate on the mechanisms responsible for this accumulation of extracellular matrix?

**Dr. Ronco:** Zhu and associates have shown that production of matrix proteins (including type-IV collagen, laminin, and fibronectin) and of bioactive TGF-\( \beta \) was increased in rat mesangial cells cultured in the presence of light chains isolated from MIDD patients [101]. Furthermore, anti-TGF-\( \beta \) antibody abolished the inhibition of cell proliferation and the increase of extracellular matrix protein production caused by these light chains. These findings were not obtained when mesangial cells were exposed to human albumin or to two other light chains previously characterized to be tubulopathic. Together with overexpression of TGF-\( \beta \) in affected glomeruli of MIDD patients, these data support a key role for TGF-\( \beta \) in extracellular matrix accumulation.

**Dr. Rossert:** If TGF-\( \beta \) is a key player, would you not expect some accumulation of type-I collagen?

**Dr. Ronco:** Certainly, yes. I should stress, however, that matrix accumulation can result from increased synthesis but also from decreased degradation of matrix components. Since type-I and type-IV collagens are degraded by different metalloproteases, one could suggest that those degrading type-I collagen (interstitial collagens) are upregulated in glomeruli of MIDD patients.
tion. Would you recommend the use of intensive chemotherapy with blood stem-cell support in MIDD patients without myeloma since this treatment seems to be promising in patients with AL amyloidosis [56]?  

Dr. Ronco: The question is more difficult to answer than in AL amyloidosis, because the prognosis of MIDD is more heterogeneous: the median survival of patients with AL amyloidosis is only 13 months from diagnosis [57], while the life span of MIDD patients extends from one month to 10 years. It is therefore necessary to define the subpopulation of MIDD patients who could benefit from treatment. Patients with severe renal complications (including nephrotic syndrome and progressive renal failure) or clinical signs of heart or liver involvement should be treated. It is not possible to affirm as yet the superiority of dose-intensive chemotherapy with blood stem-cell support over conventional chemotherapy in the absence of randomized clinical trials. However, based on the results obtained in AL amyloidosis [56], I would recommend intensive treatment in patients under the age of 60.  

Dr. Eric Rondeau (Département de Néphrologie, Hôpital Tenon): One way to inhibit abnormal protein deposition could be to prevent protein assembly in β sheet structures or other insoluble conformations. Recently Soto et al reported that small peptides with partial homology to the Aβ protein of Alzheimer’s disease were able to prevent the Aβ fibrillogenesis in vivo and to dissolve existing fibrils in vitro [103]. What do you think of such an approach in paraneoplastic glomerulopathies with abnormal protein deposition?  

Dr. Ronco: The approach developed by Soto and co-workers can theoretically apply to glomerular diseases with β-fibrillogenesis, that is, amyloidosis. The design of β-sheet breakers requires, however, that the amyloidogenic sequence in the protein precursor be known. These data are not yet available for amyloidogenic immunoglobulin light chains.  

Dr. Harrington: Did knowledge of the results of the renal biopsy affect the treatment of the patients you presented? At least in Patient 1, I suspect that the treatment would have been identical.  

Dr. Ronco: I agree that Patient 1’s treatment was not influenced by the results of the renal biopsy. In fact, in carcinoma-associated glomerulopathies, the renal disease often reveals the neoplasia; in such cases, the renal lesion, most often MGN, leads to a search for a cancer and thus dramatically affects the patient’s treatment. The finding of GOMMID in Patient 2 with a well-controlled CLL prompted us to prolong chemotherapy for three years despite the absence of enlarged lymph nodes and tumor mass and of bone marrow infiltration. Patient 3 had a low-mass myeloma that would not have required chemotherapy in the absence of renal complications.

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