Nephrotic Syndrome, Renal Failure, and Renal Malignancy: An Unusual Tumor-Associated Glomerulonephritis

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Abstract. The association between malignancy and glomerular disease has been appreciated for over three decades. Although the relationship between membranous glomerulonephritis or minimal-change nephrotic syndrome and carcinoma or lymphoma, respectively, are the most widely known, several other glomerular lesions have been described in patients with malignancy. In this article, a patient who presented with nephrotic syndrome, volume overload, and renal failure, who was subsequently found to have a renal mass, is described. Resection of the mass, which proved to be a renal cell carcinoma, led to resolution of proteinuria and improvement of renal function. Pathology on the noninvolved portion of the kidney revealed a membranoproliferative glomerular lesion, a lesion usually associated with lymphomas and not previously described with renal carcinoma. Although a role of tumor antigens and anti-tumor antibodies in producing glomerular immune deposits has been speculated upon, the evidence for this assertion was spotty. However, reports of remission of proteinuria after tumor treatment or removal support a role of tumor products in pathogenesis. Although the association between proteinuria and malignancy is rare, it should be kept in mind, particularly in older patients with membranous glomerulonephritis where the possibility of malignancy needs to be further evaluated.

Glomerular lesions associated with malignancy have been recognized for over three decades. In 1966, Lee et al. reported on the association of cancer with the nephrotic syndrome, but before that, renal involvement by amyloid in the setting of malignancy had been recognized as a paraneoplastic syndrome (1). The most common renal lesion present in that series was membranous glomerulonephritis associated with solid tumors. Other renal lesions associated with neoplasia, including minimal-change nephrotic syndrome, tubulointerstitial disease, and membranoproliferative, crescentic, focal necrotizing, and cryoglobulinemic glomerulonephritis (GN), have been described (2–3). However, renal cell carcinoma is one of the less common solid tumors associated with glomerulonephritis. In this article, we describe a case of nephrotic syndrome and renal failure in a patient subsequently found to have a renal cell carcinoma and membranoproliferative glomerulonephritis (MPGN), which improved after resection of the tumor.

Case Report

A 65-year-old man with a 10-yr history of hypertension presented to the emergency room of a local hospital, complaining of generalized weakness, progressive shortness of breath, and decreased urine output for 1 wk. The patient had noted an upper respiratory illness approximately 1 month before, with sore throat, cough, and wheezing, although a throat culture at that time was reportedly negative for β-hemolytic streptococci. Past medical history was significant for atypical chest pain with a negative exercise stress test. There was no history of transfusions, hepatitis, or intravenous drug use. On examination at the time of presentation, the patient was in mild respiratory distress, with a blood pressure of 192/108 mmHg, a pulse rate of 68, jugular venous distention, bilateral rales, and peripheral edema.

Laboratory evaluation revealed the following measurements: sodium, 136 mEq/l; potassium, 4.8 mEq/l; chloride, 102 mEq/l; carbon dioxide, 20 mEq/l; BUN, 83 mg/dl; creatinine, 3.3 mg/dl; glucose, 94 mg/dl; serum albumin, 3.3 g/dl; alkaline phosphatase, 102 U/l (normal, 20 to 125 U/l); lactate dehydrogenase, 306 U/l (normal, 0 to 250 U/l); and aspartate aminotransferase, 21 U/l (normal, 0 to 42 U/l). A complete blood cell count demonstrated a hemoglobin level of 11.2 g/dl, hematocrit value of 35%, white blood cell count of 8900/mm³, and a platelet count of 161,000/mm³. Urinalysis revealed microscopic hematuria (3+) and proteinuria (4+), with many red blood cells per high-power field on examination of the urine sediment and one to five granular casts. A 24-h urine collection revealed a total protein level of 9.4 g and a creatinine clearance rate of 50 ml/min. An antinuclear antibody test was positive at a titer of 1:160. Tests for rheumatoid factor, anti-streptolysin O, anti-double-stranded DNA, anti-ribonucleoprotein, anti-Smith, and anti-neutrophil cytoplasmic antibodies were negative. The total hemolytic complement level was 55 U/ml (normal, 100 to 300 U/ml). No cryoglobulins or other abnormal serum paraproteins were detected.

Ultrasound examination of the kidneys revealed the left
kidney to be 14.4 × 7.1 cm and the right kidney to be 13.5 × 6.9 cm without evidence of obstruction. A 5.7 × 5.0 × 5.5 cm mass was identified in the upper pole of the right kidney. Computed tomographic scan demonstrated multiple areas of calcification in this region. Chest x-ray showed bilateral pleural effusions.

The patient was treated with intravenous furosemide and Procardia XL (Pratt Pharmaceuticals Division, Pfizer Inc., New York, NY), 60 mg twice daily, with improvement in his symptoms. He was subsequently referred to our center for further evaluation and management. Repeat complement levels (C3, C4) were normal. Tests for hepatitis B surface antigen and hepatitis C antibodies were negative. The remainder of his clinical course is depicted in Figure 1. He underwent an elective nephrectomy, which was followed by transient worsening of his renal function, with his serum creatinine concentration rising to as high as 5.1 mg/dl. Subsequently, his proteinuria and renal function gradually improved. Seven months after surgery, he remains well, with a 24-h urine protein excretion value of 270 mg and creatinine clearance rate of 60 ml/min. The microscopic hematuria previously observed had resolved.

Pathology

The resected kidney measured 15 × 9 × 3 cm, with a pink-tan nodular tumor at the upper pole measuring 6 × 6 × 2 cm. The capsule overlying the tumor was adherent and stripped with difficulty. On cut-section examination, the tumor extended beyond the outer cortex. The renal pelvis, ureter, artery, and vein appeared grossly free of tumor. On microscopic examination, the tumor was classified as a renal cell carcinoma, clear-cell type, intermediate nuclear grade, with massive necrosis and extension into the renal capsule and perinephric fat.

A wedge biopsy of the normal-appearing portion of the kidney contained more than 100 glomeruli, 20% showing global sclerosis and 3% segmental sclerosis. Focal areas of cortical scarring, with global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and mononuclear infiltrate were present. In the remaining cortex, glomeruli showed variable narrowing of the capillary lumina as a result of moderate increase in mesangial matrix and diffuse intracapillary cellular proliferation, with lobular accentuation. There was a thickening of the glomerular basement membranes, with peripheral extension of the mesangium and double contouring of basement membranes (Figure 2, A and B). This was accompanied by mild neutrophil infiltration. Segmental cellular to fibrocellular to fibrograding crescents were present in approximately 10% of glomeruli and segmental adhesions to Bowman’s capsule in another 5%. Visceral epithelial cells were markedly swollen and contained several large hyaline droplets in foci. The interstitium showed mild tubular atrophy and interstitial fibrosis, with patchy mononuclear cell infiltration. The arteries and arterioles showed mild to focally moderate intimal thickening, with corresponding luminal narrowing. Immunofluorescence microscopy showed 1 to 2+ granular and focal semilinear staining along the glomerular capillary walls for immunoglobulin (Ig) G, and complements C1q and C3. Trace deposits of IgM and IgA were also present.
This lesion was classified as an immune complex-mediated glomerulonephritis, with a membranoproliferative pattern of injury. Electron microscopy confirmed the presence of deposits, although the predominant distribution was subepithelial, with few intramembranous and subendothelial deposits (Figure 2B). No hump-like deposits characteristic of post-infectious GN were seen.

Discussion
This patient presented with the fairly rapid development of symptoms related to fluid retention and was found to have nephrotic syndrome with significant loss of renal function in a setting that was initially felt to be consistent with a post-infectious GN. Further examination failed to reveal evidence of previous streptococcal infection but did demonstrate a renal mass. These circumstances suggested the likelihood of a tumor-related glomerular lesion, leading to the nephrotic syndrome and renal failure (Table 1).

Membranous GN is the glomerular lesion that has been described most often in patients with neoplasia (1–3). Several studies have noted an approximately 10% prevalence of neoplasia in patients with membranous GN (1,2,4,5), although other studies have not confirmed this high value and have questioned the significance of the association (3). The most common solid tumors associated with membranous GN are those of the lung, gastrointestinal tract, and breast. Although membranous GN has been described in association with renal cell carcinoma, it is a rare association. The development of membranous GN, an immune complex-mediated form of glomerular injury, in these patients has been proposed to be the result of deposition of tumor-associated antigens and anti-tumor antibodies in the glomerulus or to alterations of immune function in patients with malignancies that render the patient more susceptible to the development of immune complex injury initiated by endogenous or exogenous antigens (2,3,5). Although some investigators have succeeded in demonstrating tumor-related antigens and antibodies in deposits (reviewed in References 3 and 5), other studies have been negative, and the overall rigor and sophistication of these early studies is problematic. Although one study reported the presence of antibody to renal tubular epithelial antigens in deposits from patients with renal cell carcinoma, these patients did not have a membranous lesion, and another group failed to find evidence of tumor or renal tubular epithelial reactive antibodies in a patient with renal cell carcinoma and membranous GN (6,7). Thus, the pathogenesis of the immune deposits in these cases remains unresolved. Reports of resolution of the nephrotic syndrome with successful treatment or resection of the malignancy, however, lend support to the theory that tumor-related products are important in pathogenesis (8).

Another potential cause of nephrotic syndrome and renal failure in a patient with a renal cell carcinoma is the development of amyloidosis. Approximately 2 to 3% of cases of renal cell carcinoma are complicated by systemic amyloidosis and 25 to 33% of carcinomas associated with amyloidosis are of renal origin (9,10). Renal involvement is present in approximately 80% of cases of cancer-associated amyloidosis, and the spleen and liver are commonly involved as well (10). Proteinuria, nephrotic syndrome, and elevations of BUN are also commonly present (10). Because the amyloidosis in these cases is of the AA type, the most likely etiology is increased production of acute-phase reactants and chronic inflammation because of the tumor. Of interest in this patient is the presence of significant hypertension, a finding that is generally absent in patients with amyloidosis secondary to malignancy and in secondary amyloidosis in general. Thus, on clinical presentation alone, amyloidosis would be a less likely diagnosis in this case. Remission of nephrotic syndrome associated with tumor-related amyloidosis has also been reported after resection of the tumor (9,11).

Several other glomerular lesions have been described in association with solid tumors, including carcinomas and lymphomas, and could present with the clinical course seen here. Rapidly progressive (crescentic) glomerulonephritis has been found to be associated with malignancy in 7 to 9% of cases, one of which was a renal carcinoma (12,13). There have also been several reported cases in association with lymphoma (3). Immune-complex deposits were unusual in one study (12) but were common in the other (13), suggesting a heterogeneous group of pathogenetic mechanisms. IgA GN has also rarely been described with renal cell carcinoma (14,15). Wilms' tumor, the most common renal malignancy of childhood, has also been described in association with glomerular lesions. Thorner et al. found 25 cases described in the literature, with glomerular lesions including minimal-change nephrotic syndrome, focal glomerulosclerosis, membranous and MPGN, although the significance of these associations is unclear (16). Finally, a case of minimal-change nephrotic syndrome that resolved after tumor resection has been described in a patient with a renal oncocytoma, a rare renal tumor believed to be of proximal tubular origin (17).

Lymphoid malignancies are another well-recognized cause of glomerular lesions, although again the significance of the association has been questioned (3). The association of Hodgkin's disease with minimal-change nephrotic syndrome is well documented, although rare (2,3). Other glomerular lesions

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Table 1. Glomerular lesions associated with renal tumors

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<th>Renal cell carcinoma</th>
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<tr>
<td></td>
<td>membranous glomerulonephritis (1–8)</td>
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<td>immunoglobulin A glomerulonephritis (14,15)</td>
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<td>minimal-change nephrotic syndrome (6)</td>
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<td>Wilms' tumor</td>
<td>membranoproliferative glomerulonephritis (16)</td>
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<td>Renal oncocytoma</td>
<td>minimal-change nephrotic syndrome (17)</td>
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* Reference citations shown in parentheses.
reported in lymphomas and leukemias include focal glomerulosclerosis, MPGN, amyloidosis, IgA nephropathy, and crescentic glomerulonephritis (reviewed in Reference 3). MPGN is the single most common glomerular lesion in patients with chronic lymphocytic leukemia (3). Abnormal serum proteins may also contribute to glomerular injury, resulting in primary amyloidosis, light- or heavy-chain deposit disease, and cryoglobulinemic GN in association with plasma cell dyscrasias and other lymphoid malignancies.

The membranoproliferative pattern of glomerular injury, defined by light microscopy, can be seen in idiopathic MPGN (types I, II, and III), and in several other conditions, including bacterial endocarditis, shunt infections, visceral abscesses, other chronic infections, chronic thrombotic microangiopathies, and paraproteinemias (reviewed in Reference 18). What is common to many of these conditions is the presence of persistent antigenemia, autoimmune reactivity, or paraproteins, all of which may result in the persistent presence of circulating immune complexes. The most common causes of persistent antigenemia include chronic viral, bacterial, and protozoal infections (18). What is not clear is why this pattern of injury is so much more common in chronic infections than in malignancies, although its occurrence in malignancy may be the result of a similar pathogenetic mechanism.

The patient presented here is unusual in that the association of MPGN with malignancy has been most commonly with lymphoplasmacytic disorders, especially chronic lymphocytic leukemia (3). This histologic appearance is rare among the glomerular lesions associated with cancer, although the original report of Lee et al. mentioned one patient with a lobular GN in association with adenocarcinoma of the kidney and monocytic leukemia (1). Even though electron microscopy of our patient’s kidney showed a predominance of subepithelial deposits, the presence of intracapillary proliferation and circumferential mesangial interposition clearly differentiate this case from membranous GN. The lack of subepithelial humps, as well as the presence of frequent peripheral extension and circumferential interposition of mesangium and reduplication of the glomerular basement membrane, argue against the presence of a post-infectious GN. Furthermore, evidence of antecedent streptococcal infection and of circulating paraproteins was not found. The case presented here does not fit neatly into a type I or III pattern of MPGN because of the absence of subendothelial deposits on electron microscopy. The presence of areas of semilunar staining along the glomerular capillary wall on immunofluorescence, however, suggests subendothelial deposits. Absence of identifiable subendothelial electron dense deposits on electron microscopy, despite the presence of deposits on immunofluorescence, has previously been described in MPGN (19). Thus, a type III pattern of MPGN, with subendothelial and subepithelial immune deposits, appears to be most likely.

Although proteinuria and nephrotic syndrome are relatively rare in patients with malignancy (approximately 1%), the overall prevalence of malignancy in patients with nephrotic syndrome has varied from close to zero to as high as 22% (3,5). These widely varying estimates have led some authors to argue against a full malignancy examination in all such patients (3), whereas others have stressed the need to be cognizant of this association and to screen patients, especially those over the age of 60 (2,4,5). Because most cases of glomerular disease in association with malignancy, with the exception of minimal-change nephrotic syndrome with lymphoma, are of the immune-complex variety, a contribution of tumor or other endogenous or exogenous antigens plus an immune response that does not result in effective antigen clearance seem likely to be important in the pathogenesis. The prognosis of patients with malignancy and nephrotic syndrome appears to be much worse overall (2), although again the rarity of these patients makes definitive study of this question difficult. The possibility of remission of proteinuria and/or renal failure after successful treatment of the malignancy should favor such treatment whenever possible.

References
The Training Program in Nephrology at New York Medical College, Westchester Medical Center

Postgraduate training in nephrology at the Westchester Medical Center began in 1965 and became affiliated with New York Medical College in 1970. Over 50 fellows have been trained and are currently pursuing careers in academic medicine and private practice of nephrology. The program accepts two to three fellows per year and provides 2 years of training, with an optional third year for those desiring more prolonged research exposure. Clinical training occurs on a very busy inpatient and consultative nephrology service at a tertiary and quaternary care academic medical center. Approximately 600 inpatient consults are seen per year, and 4000 acute inpatient dialysis treatments are performed under direct supervision of fellows and faculty. Fellows develop experience with all dialysis modalities, including acute hemodialysis, peritoneal dialysis, continuous arteriovenous hemodialysis and continuous venovenous hemodialysis. Fellows also rotate on the renal transplant service, which performs over 125 transplants per year and is the largest renal transplant program in New York State. Outpatient dialysis is performed at two hospital-associated and one satellite dialysis center with over 40,000 treatments per year. Home dialysis training, including home hemodialysis and continuous ambulatory peritoneal dialysis, are also available. Ambulatory-care training in nephrology is accomplished in a faculty practice and outpatient clinic setting, with approximately 1400 patient visits per year. Fellows have the opportunity to follow-up patients continuously throughout their training.

The division is composed of eight full-time faculty members with varying interests. Fellows participate in divisional research projects under the supervision of a faculty member. Current areas of research interest include mechanisms of glomerular injury, pregnancy-associated renal disease and hypertension, hypertension control in chronic hemodialysis patients, cardiac hypertrophy and remodeling in hypertension and uremia, the role of cytochrome P<sub>450</sub> enzymes in renal carcinogenesis, and the diagnosis and treatment of transplant rejection.