OVERVIEW OF THE NEPHROLOGY TRAINING PROGRAM
THE UNIVERSITY OF ARIZONA HEALTH SCIENCES CENTER AND
TUCSON VETERANS ADMINISTRATION MEDICAL CENTER

The University of Arizona offers both 2- and 3-yr clinical and research training programs in nephrology. These programs are designed to prepare physicians for careers in clinical practice or academic medicine. Extensive training in all aspects of clinical nephrology is provided in two diverse hospitals, an outpatient dialysis center, and a rapidly growing transplantation service. The research program provides a variety of opportunities, and disciplines include renal physiology and pathophysiology, dialysis physiology, transport, molecular biology, microcirculation, and nuclear magnetic resonance.

Fellows rotate through the University Medical Center, the Tucson Veterans Administration Medical Center, and the Desert Dialysis Center. The University Medical Center is a tertiary-care hospital with kidney, liver and heart transplantation, inpatient dialysis, and consultative nephrology. The Tucson Veterans Administration is a referral center, with both ambulatory and inpatient dialysis, consultative nephrology, and a large nephrology-hypertension outpatient service. Desert Dialysis, the outpatient dialysis center, has 80 hemodialysis and 30 peritoneal dialysis patients. Fellows may elect to rotate through pediatric nephrology at the University Medical Center. Because of our geographic location, we are exposed to most of the ethnic groups of North America and therefore have experience with a wide variety of pathologies. Skills are developed in all aspects of dialysis, renal biopsy, and management of renal transplant recipients.

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Fellows who decide to take the research track have 2 years of protected research time after 1 year of clinical training, thus providing training in basic and clinical research. This program allows for the acquisition of the scientific techniques and skills necessary to conduct independent research and pursue an academic career.

Acute Renal Failure in Membranous Glomerulonephropathy: A Result of Superimposed Crescentic Glomerulonephritis

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ABSTRACT

A patient who presented with acute renal failure and anasarca secondary to crescentic glomerulonephritis superimposed on existing membranous glomerulonephropathy of 15 years' duration is described. The patient responded to an initial course of prednisone but failed to respond to a second course after relapse. The differential diagnosis of acute renal failure in the setting of nephrotic syndrome is discussed. Eighteen cases of crescentic glomerulonephritis superimposed on membranous glomerulonephropathy are reviewed. The clinical setting is heterogeneous with variable presentation and outcome. It appears that patients without antiglomerular basement membrane antibodies have a better prognosis than those who have antibodies. Patients with membranous glomerulonephropathy who develop unexplained acute renal failure should undergo early renal biopsy in order to rule out unexpected pathologic complications.

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Idiopathic membranous glomerulonephropathy (MGN) may run a variable course and in a significant number of patients does not require specific treatment (1,2). Renal failure usually develops gradually in patients with MGN and only rarely is complicated by acute renal failure (ARF) (3). We describe a patient with nephrotic syndrome (NS) secondary to MGN who developed ARF 15 yr later as the result of superimposed crescentic glomerulonephritis (CGN). CGN causing ARF in patients with MGN was first reported by Klassen et al. in 1974 (4). The development of CGN superimposed on MGN is a rare complication—only 17 cases have been documented in the literature (4–18)—but should be considered whenever MGN is complicated by ARF.

CASE REPORT

A 67-yr-old white man was admitted to the University Medical Center on January 21, 1993, for increasing generalized swelling. He had been diagnosed as having NS secondary to MGN in 1977. At that time, his serum creatinine level was 1.2 mg/dL and his urine protein value was 14 g/24 h. A renal biopsy, in which 20 glomeruli were obtained, had demonstrated enlarged glomeruli with thickened glomerular basement membranes (GBM) and patent capillary loops (Figure 1A). Immunofluorescence had revealed diffuse, finely granular deposits of immunoglobulin (Ig) M, IgG, and C3 along the capillary loops. Electron microscopy had shown electron-dense deposits within the subepithelial space (Figure 1B). The patient had been treated with prednisone and azathioprine for a period of 18 months. His proteinuria had persisted and ranged from 3 to 8.2 g/24 h up until April 1983 (6 yr later), when it had spontaneously dropped to 1.8 g/24 h. Thereafter, it had remained below 500 mg, and in January 1988 (a further 5 yr later), his urine protein level had been measured at 60 mg/24 h. During this five-year period, his serum creatinine remained within the normal range.

In 1988, rectal cancer and colon polyps had been diagnosed and the patient had undergone a colectomy and ileostomy followed by radiation therapy. Thereafter, he had remained cancer free. In 1992, after a gastrointestinal bleed, extensive evaluation of the patient for neoplasm had failed to demonstrate recurrent disease. His serum creatinine level had been measured at 1.2 mg/dL.

In November 1992, he had undergone coronary angiography, which was complicated by a transient rise in his serum creatinine level from 2.0 to 3.8 mg/dL. In December 1992, after coronary artery bypass surgery, the patient had complained of progressive symptoms of fluid retention. On December 30, 1992, a transurethral prostatectomy had been performed for benign prostatic hypertrophy. The postoperative course had been complicated by an enterobacter urinary tract infection, for which the patient had received a course of ciprofloxacin. The patient's serum creatinine level had remained at 2.0 mg/dL.

On the 21st of January 1993, the patient was admitted to our unit complaining of a weight gain of 4.5 kg in the preceding week and 14 kg since the coronary artery bypass surgery. Physical examination revealed severe anasarca and a blood pressure of 156/96 while lying and 110/72 while standing. Stool in the ileostomy pouch tested guaiac-positive. Urine analysis showed a specific gravity of 1.015 and 3+ protein, and 2+ blood on dipstix. Microscopic examination of the sediment revealed oval fat bodies and fatty casts. There were 3 red blood cells and 37 white blood cells per high-power field. Urine Wright's stain for eosinophils was negative. The hematocrit value was 25.9%.
The white blood cell count was 10,800 without eosinophilia. The serum creatinine was 3.2 mg/dL, and serum albumin was 1.2 g/dL. Twenty-four-hour urine protein level was 14.8 g, and the creatinine clearance was 35 mL/min per 1.73 m². Complement levels were low: C3 of 44 (80 to 180 mg/dL) and C4 of 11 (15 to 45 mg/dL). Serology for antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins, hepatitis B surface antigen, anti-GBM antibodies, antistreptococcal antibodies, and blood cultures were all negative. Both serum and urine protein electrophoresis failed to demonstrate a monoclonal component. Doppler ultrasonography excluded obstructive uropathy or renal vein thrombosis from the differential diagnosis. The right kidney measured 11.2 cm, and the left measured 11 cm.

Despite a brisk diuresis in response to blood transfusion and intravenous albumin and furosemide infusion, there was a progressive rise in the creatinine level from 3.2 to 5.5 mg/dL. As a result, a renal biopsy was obtained on January 28, 1993. In the specimen submitted for light microscopy, there were nine glomeruli, of which two were obsolescent. Capillary walls appeared thickened, and there was an increased mesangial cellularity with neutrophils within the capillary tuft. Four of seven viable glomeruli demonstrated cellular crescents (Figure 2A). There was a cellular infiltrate with mononuclear cells and eosinophils in the interstitium. A moderate degree of interstitial fibrosis was noted. Immunofluorescence demonstrated diffuse, finely granular staining of IgA, IgG, and C3 along the capillary wall. Electron microscopy demonstrated extensive small to moderate-sized subepithelial electron-dense deposits (Figure 2B). The histology was consistent with MGN with superimposed CGN, as well as possible allergic interstitial nephritis.

On the basis of the histologic finding of CGN and possible allergic interstitial nephritis, presumably due to ciprofloxacin (which was discontinued on admission), it was decided that the patient would be treated with intravenous pulse methylprednisolone, 1 g/day, for 2 days, followed by oral prednisone, 1 mg/kg per day. The patient required hemodialysis 3 days after the biopsy. One month later, while still on oral prednisone, he had regained sufficient renal function to withdraw from dialysis. His creatinine level was 3.7 mg/dL, and the creatinine clearance was 35 mL/min per 1.73 m². The prednisone dose was tapered off over 3 months, and in June 1993, the serum creatinine level was 2.1 mg/dL. The patient was lost to follow-up and was readmitted in October 1993 with oliguria, a serum creatinine level of 7.7 mg/dL, and a 24-h urine protein value of 19.8 g. Pulse steroid therapy was reinstituted and thereafter converted to oral prednisone. He failed to recover renal function and had to be placed on the chronic hemodialysis program. Ten months subsequent to the initiation of dialysis, metastatic cancer of the colon was diagnosed. During palliative tumor removal, the obstructed right kidney was resected. Renal histology demonstrated a diffusely scarred kidney with persistent features of MGN in the few viable glomeruli.

**DISCUSSION**

Our patient had transformed from a benign stable form of MGN to MGN complicated by a superimposed CGN associated with low complements. He presented with rapid deterioration of renal function and anasarca. Intravenous volume expansion failed to reverse the ARF. In retrospect, allergic interstitial nephritis was unlikely to be the sole cause of the ARF because of the recurrence of renal failure 3 months after the prednisone was stopped.

In patients with preexisting NS, the differential diagnosis of ARF is diverse (Table 1). A prerenal state may occur secondary to the diminished intravascular volume as a result of the hypoalbuminemia (3). Decreased GFR may be further aggravated by the use of diuretics and/or nonsteroidal anti-inflammatory drugs, surgical procedures, and acute blood loss (3).
This form of ARF can be reversed by drug withdrawal and the reestablishment of effective intravascular volume, provided therapy is initiated within a critical period of renal hypoperfusion. Progression of this form of prerenal azotemia may induce ischemic acute tubular necrosis. The restoration of renal perfusion may or may not result in a complete recovery.

Renal interstitial edema in NS that occurs secondary to decreased plasma oncotic activity may cause ARF. As proposed by Lowenstein et al. (19), the interstitial edema increases hydrostatic pressure in the Bowman’s space and the proximal convoluted tubule, subsequently decreasing ultrafiltration pressure and GFR. This form of ARF responds to albumin infusion and diuresis by decreasing the edema and reestablishing ultrafiltration pressure (19).

Renal vein thrombosis may complicate NS and result in ARF. It occurs most frequently in MGN (3). Renal failure occurs in the setting of bilateral renal vein thrombosis or in single-vein thrombosis in patients who already have renal dysfunction. Patients with NS are predisposed to thrombosis because of the hypercoagulable state secondary to antithrombin III deficiency, a generalized increase of clotting factors, and an increased platelet activity (20). The loss of antithrombin III in the urine results in the renal vein blood having the lowest concentration of antithrombin III. Further, renal vein blood is also hemoconcentrated, thus increasing the predisposition to thrombosis. Recommended therapy is anticoagulation, in view of a high incidence of pulmonary embolus (21).

In patients with NS, interstitial nephritis may cause ARF, which occurs most commonly in the setting of drug administration. Drugs commonly encountered in patients with NS are nonsteroidal anti-inflammatory drugs, diuretics and various antibiotics. The presence of white blood cells in the urine, and eosinophils specifically in both the urine and the blood, would be a strong indicator of this diagnosis.

Obstructive uropathy is another common cause of ARF that should be listed in the differential diagnosis of NS patients. Confirmation of obstruction is best made by renal ultrasound and, when found, should be relieved as soon as possible.

Last, the possibility of superimposed glomerulonephropathy needs to be considered. Acute glomerulonephritis (GN), IgA nephropathy, mesangiofatic GN, cirrhotic glomerulosclerosis, CGN, and diabetic nephropathy have all been described in association with MGN (8,18). Crescentic GN associated with acute postinfectious GN, occult abscess, neoplasm, collagen vascular disease, vasculitis, Goodpasture’s syndrome, and anti-GBM glomerulonephritis may result in ARF. Thrombotic microangiopathies such as thrombotic thrombocytopenic purpura or hemolytic uremic syndrome may result in ARF when superimposed on MGN.

We summarized 18 cases of CGN superimposed on MGN from 15 articles in the literature, along with this case, in Table 2 (4–18). Analysis revealed that this condition occurs in males to females in a ratio of 2:1, which is not different from the gender ratio of MGN (2). The average age was 43 ± 15 yr with a range between 16 and 67. Eleven of the 18 patients had documented preexisting MGN. Time from the diagnosis of MGN to the development of CGN was 39 ± 49 months (range 6 to 180 months). Blood pressure was recorded in 13 patients. Among these patients, seven were hypertensive. Twenty-four-hour urine protein levels ranged from 0.3 to 15.1 g in 15 patients, with 7 in the nephrotic range. Presentation was frequently associated with extrarenal complicating factors. Two patients had a history of exposure to chemical solvents— one to a wood primer with copper sulfate as its active ingredient, and the other to a petroleum-based solvent. Both of them had anti-GBM glomerulonephritis, which is known to be associated with chemical solvent exposure. Three patients had a viral syndrome before presentation. One patient had pulmonary sarcoidosis, one had rectal crypt abscesses, and one had gastroenteritis. Our patient had rectal cancer diagnosed 5 yr before presenting with CGN. Recurrent disease was detected 10 months after the initiation of dialysis. CGN has been described in conjunction with carcinoma (22). Five of the seven cases reported had complement levels measured, all of which were within the normal range. Serologic tests for hypocomplementemia-related glomerulonephritides failed to detect a cause for the low complement in our patient. As a result, his hypocomplementemia remains unexplained.

Six of 15 patients had anti-GBM antibodies, including two who had the IgG anti-GBM antibodies eluted off the basement membrane of their renal biopsy. Findings on immunofluorescence of the renal biopsies included diffuse granular staining of the capillary loop with IgG and C3. Eight of the 14 patients reported also had some IgM and IgA deposits in the same distribution. One patient who had anti-GBM antibodies had mixed linear and granular deposits noted along the basement membrane.
TABLE 2. Crescentic glomerulonephritis complicating primary membranous glomerulonephropathy

<table>
<thead>
<tr>
<th>Study (1st Author)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Preexisting MGN</th>
<th>Associated Factors</th>
<th>Anti-GBM Antibodies</th>
<th>Proteinuria (g/24 h)</th>
<th>Blood Pressure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klaassen (4)</td>
<td>49</td>
<td>M</td>
<td>8</td>
<td>CS</td>
<td>+</td>
<td>1.1</td>
<td>140/80</td>
<td>Death</td>
</tr>
<tr>
<td>Nicholson (5)</td>
<td>50</td>
<td>F</td>
<td>12</td>
<td></td>
<td>+</td>
<td>1.2</td>
<td>200/100</td>
<td>Death</td>
</tr>
<tr>
<td>Moorthy (6)</td>
<td>53</td>
<td>M</td>
<td>13</td>
<td>CS</td>
<td>+</td>
<td>3</td>
<td>150/90</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Moorthy (6)</td>
<td>44</td>
<td>M</td>
<td></td>
<td>GE</td>
<td>+</td>
<td>4</td>
<td>150/90</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Moorthy (6)</td>
<td>55</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td>1.6</td>
<td>158/86</td>
<td>Recovery</td>
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<tr>
<td>Hill (15)</td>
<td>33</td>
<td>F</td>
<td>36</td>
<td></td>
<td></td>
<td>5.5</td>
<td>130/100</td>
<td>Transplantation</td>
</tr>
<tr>
<td>Kent Taylor (13)</td>
<td>57</td>
<td>M</td>
<td>Sarcoid</td>
<td></td>
<td></td>
<td>1.5</td>
<td>180/94</td>
<td>CRI</td>
</tr>
<tr>
<td>Mitas (12)</td>
<td>40</td>
<td>M</td>
<td>Sepsis</td>
<td></td>
<td></td>
<td>.3</td>
<td>CRI</td>
<td></td>
</tr>
<tr>
<td>Abreo (7)</td>
<td>17</td>
<td>F</td>
<td>34</td>
<td>VS</td>
<td></td>
<td>2.4</td>
<td>125/70</td>
<td>CRI</td>
</tr>
<tr>
<td>Koethe (10)</td>
<td>16</td>
<td>F</td>
<td>72</td>
<td></td>
<td></td>
<td>3.7</td>
<td>210/120</td>
<td>Recovery</td>
</tr>
<tr>
<td>Richman (17)</td>
<td>65</td>
<td>M</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Tateno (9)</td>
<td>39</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>130/80</td>
<td>Recovery</td>
</tr>
<tr>
<td>Gerhard (16)</td>
<td>42</td>
<td>F</td>
<td></td>
<td>VS</td>
<td></td>
<td>15.1</td>
<td>190/110</td>
<td>Recovery</td>
</tr>
<tr>
<td>Nguyen (11)</td>
<td>24</td>
<td>M</td>
<td>17</td>
<td>RVT</td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Kurki (14)</td>
<td>54</td>
<td>M</td>
<td>24</td>
<td>VS</td>
<td>+</td>
<td>5</td>
<td>Transplantation</td>
<td></td>
</tr>
<tr>
<td>Monga (8)</td>
<td>49</td>
<td>M</td>
<td>3.5</td>
<td>160/100</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertani (18)</td>
<td>26</td>
<td>M</td>
<td>24</td>
<td>Rectal cancer</td>
<td>14.8</td>
<td>156/96</td>
<td>Recovery/</td>
<td></td>
</tr>
<tr>
<td>This Case</td>
<td>67</td>
<td>M</td>
<td>180</td>
<td>Dialysis</td>
<td>5.5</td>
<td>130/100</td>
<td>Dialysis</td>
<td></td>
</tr>
</tbody>
</table>

Twelve of 18 patients progressed to end-stage renal failure within 1 yr of the diagnosis of CGN. Five died, one from heart failure and four from renal failure. All six patients with anti-GBM antibodies developed end-stage renal failure. Four patients recovered, one had a spontaneous recovery, and our patient relapsed after discontinuing therapy. Three patients had chronic renal insufficiency but did not require dialysis. None of these seven patients had anti-GBM antibodies detected in their serum. The approach to therapy was different in the cases reported. Most patients were given steroid therapy; some received chemotherapy and/or plasmapheresis. It was not possible to determine from the outcome of these patients whether therapy was of value or not.

In summary, patients with CGN superimposed on MGN are a heterogenous group with variable clinical presentation and course. It is likely that the pathogenesis of their CGN varies. The pathogenesis of superimposed glomerulonephropathy is thought to be in some way related to the underlying primary renal lesion, but is not understood (8, 18). Renal failure evolves rapidly after the superimposition of the second glomerulonephropathy (18). Two-thirds of the reported cases did not have anti-GBM antibodies. These patients appear to have a better prognosis than do those with anti-GBM antibodies. However, the number of cases is too small to verify this conclusion. Other clinical findings, such as hypertension and nephrotic-range proteinuria, fail to predict the outcome.

The patient described had an unusual presentation of ARF secondary to CGN superimposed on MGN that had preexisted for 15 yr. He responded to prednisone initially but then failed to respond to a second course after a relapse. Patients who develop unexplained ARF, in the setting of MGN, should have early repeat renal biopsy to exclude unexpected complicating pathology.

REFERENCES