Ureteral Stenosis Due to Recurrent Wegener's Granulomatosis After Kidney Transplantation

Lisa M. Rich, and Walter F. Piering

Ureteral stenosis due to recurrent Wegener's granulomatosis can be manifested by obstructive uropathy due to granulomatous vasculitis. This report describes a case of ureteral obstruction in a patient who developed recurrent Wegener's granulomatosis after kidney transplantation.

The ureter is an unusual location for lesions of Wegener's granulomatosis (WG). A patient in whom recurrence of WG after kidney transplantation was suggested by obstructive uropathy due to granulomatous vasculitis (WG) at the ureterovesicle anastomosis, as well as nasal and lung involvement, is reported. The occurrence of WG in the ureter in relation to the processes causing ureteral obstruction and the recurrences of WG after kidney transplantation and its treatment are briefly reviewed.

Key Words: Vasculitis, cyclophosphamide

A 25-yr-old woman was first evaluated in April 1975 and was considered to have rheumatoid arthritis on the basis of a 1-month history of fever, fatigue, weakness, and a symmetrical polyarthritis together with a positive latex agglutination for rheumatoid factor. After aspirin therapy failed, she was treated with gold sodium thiomalate, 50 mg im twice weekly, and prednisone, 60 mg/day. Fever persisted,
along with a serum creatinine of 336 μmol/L (3.8 mg/dL) and urea of 24.6 mmol/L (69 mg/dL), rising over a week to 655 μmol/L (7.4 mg/dL) and 40.7 mmol/L (114 mg/dL), respectively. The initial urinalysis showed a 1+ test for protein. The urine sediment contained many red blood cells and white blood cells together with a few hemoglobin and red blood cell casts, oval fat bodies, hyaline, and granular and waxy casts. Gold therapy was stopped, and prednisone therapy was continued. Over the ensuing 7 months, her serum creatinine decreased, reaching 354 μmol/L (4.0 mg/dL) in March 1976. Intermittent fever persisted. A kidney biopsy was performed in April 1976 (Figure 1). Light microscopy revealed many hyalinized glomeruli. Some glomeruli exhibited crescents together with marked periglomerular infiltration of lymphocytes and plasma cells. There was vasculitis of small arterioles. Immunofluorescence microscopy revealed granular deposition of immunoglobulin (IgG), IgA, IgM, complement, and fibrin in the glomeruli. Electron microscopy showed effacement of the foot processes, irregular widening of the glomerular basement membrane, increased mesangial matrix, and no immune deposits. Her kidney function continued to decline, despite prednisone therapy, with her serum creatinine rising to 973 μmol/L (11.0 mg/dL). She developed rhinorrhea and otitis media. A biopsy of her nasal mucosa in October 1977 showed granulomas, establishing the diagnosis of Wegener's granulomatosis (WG) (Figure 2A). Shortly thereafter, she developed a "saddle nose" deformity. Cyclophosphamide (125 mg/day) was begun in October 1977 while prednisone (20 mg every other day) was continued. Although her arthritis and rhinorrhea improved dramatically with this treatment, her kidney failure worsened progressively and she began hemodialysis on March 20, 1978.

On October 16, 1978, she received a cadaveric kidney transplant. Her initial maintenance immunosuppressive therapy included azathioprine, 125 mg daily, and methylprednisolone, in a tapering dose to 24 mg/day. She had several early acute rejection episodes, each of which was successfully treated with iv bolus prednisolone.

In February 1979, she was rehospitalized because of fever, a recurrent purulent nasal discharge, and the development of a cavity in the middle lobe of her right lung. Cultures performed at the time of bronchoscopy were negative, and a transbronchial biopsy showed nonspecific inflammation. Her serum creatinine rose from 150 to 354 μmol/L (1.7 to 4.0 mg/dL). Recurrent glomerular disease was felt to be unlikely with a 24-h urine protein of 293 mg/day and urinalysis showing only hyaline casts. An iv urogram demonstrated hydronephrosis in the transplanted kidney. Cystoscopy demonstrated proliferation of tissue at the ureterovesicle junction that caused ureteral obstruction. An excisional biopsy of this lesion relieved the obstruction and demonstrated necrotizing granulomas consistent with recurrent WG (Figure 2B). Her serum creatinine fell to 177 μmol/L (2.0 mg/dL) after relief of the ureteral obstruction. Her immunosuppression was then modified to include cyclophosphamide (100 mg/day) together with prednisolone (24 mg/day) and azathioprine (25 mg/day). The cavity in her lung resolved, and her nasal dis-
Treatment with steroids had some effect, approximately doubling the survival time. When cyclophosphamide was added, 80% of patients survived for at least 1 year (1). Since then, adequate cytotoxic treatment with cyclophosphamide and prednisone has allowed prolonged survival for many patients. The National Institutes of Health experience indicated that about 10% of patients with WG develop end-stage kidney disease (2). Such patients, who are otherwise well, may be candidates for kidney transplantation.

CLINICAL AND PATHOLOGIC PRESENTATION

Wegener initially described patients with a necrotizing granulomatous arteritis of the upper and lower respiratory tracts. To date, the cause of the disease remains a mystery. There is no known correlation with any environmental or infectious agent. The disease occurs predominantly among white adults, with an average age of onset of 41 yr. Recent reviews indicate an equal sex distribution (2), although earlier reports had suggested a male predominance.

The clinical presentation is variable, but hallmarks are involvement of the upper and lower respiratory tract, including the nose, sinus, trachea, and ear, as well as pneumonitis or pulmonary nodules. The next organ most commonly involved is the kidney. Eighteen percent of patients present with glomerulonephritis, and 77% develop glomerulonephritis within 2 yr of diagnosis (2). Many patients have arthralgia or myalgias. Fever and weight loss are common. About half have some ocular involvement. Skin lesions, including purpura, or ulcers may develop. Neurologic symptoms including mononeuritis multiplex are also seen.

General laboratory findings include leukocytosis, thrombocytosis, and anemia. The erythrocyte sedimentation rate is elevated, and there may be positive tests for rheumatoid factor in about 50% of patients (3). A recent diagnostic advance has been the detection of ANCA. There are two patterns, cytoplasmic ANCA and perinuclear ANCA. The cytoplasmic pattern has a high sensitivity for WG, being positive in about 90% of patients with active disease (2). The perinuclear pattern is positive in only 5% of WG patients (2). Normal controls and controls with other vasculitides are not ANCA positive, indicating a high specificity.

REVIEW OF LITERATURE

Ureteral obstruction can occur because of luminal blockage, because of lesions within the ureteral wall, or because of compression from extrarenal masses. Mechanisms of luminal blockage include stones, sloughed papillae, or clots. External compres-
sion may be due to vascular lesions, mass lesions of the uterus and ovaries, inflammation of gastrointestinal tract structures, tumors, or retroperitoneal disease. Vasculitis is a rare cause of ureteral obstruction because of the involvement of the ureteral wall. In addition to WG, there are case reports of ureteral obstruction related to polyarteritis nodosa, Henoch-Schoenlein purpura, systemic lupus erythematosus, Churg-Strauss vasculitis, dermatomyositis, and rheumatoid nodules (4). Such lesions are found after azotemia or oliguria develops, and hydronephrosis is detected.

Five cases of WG involving the ureter, including the case presented here, have been reported (5–8) (Table 1). The patients ranged in age from 29 to 50 yr. Three were men, and two were women. All had hydronephrosis, and all had surgical intervention to relieve the obstruction. All of the patients were also treated with cyclophosphamide and prednisone and responded well. Follow-up ranged from 4 months to 15 yr.

A further review of the literature disclosed 10 patients, including the case presented here, with recurrent WG after kidney transplantation (9–17) (Table 2). Three of these 10 patients did have relapse of WG before transplantation while on dialysis. This observation refutes the proposal that the immunosuppression of uremia or dialysis prevents the activation of WG (18). The time to recurrence after transplantation ranged from 15 days to 45 months. The time to recurrence in our patient was 4 months. The location of recurrence varied and included the transplanted kidney in 4 of the 10 patients; only the case presented here involved the ureter. The age at onset of WG ranged from 10 to 38 yr, with a mean of 29 yr, somewhat younger than the average patient with WG. Seven were men, and three were women.

WG has recurred with all of the standard transplantation immunosuppressive regimens (azathioprine and prednisone alone or with cyclosporine). Four of 10 patients with recurrent WG received azathioprine and prednisone, whereas 6 patients received cyclosporine and prednisone. The remaining patient received all three drugs. Cyclophosphamide was not included in the initial maintenance immunosuppressive therapy for any of them. Nine of the 10 patients subsequently were treated with cyclophosphamide and prednisone to control the recurrence. The remaining patient was felt to be too ill to withstand additional immunosuppression and underwent removal of the kidney graft. Six of nine patients including our patient, responded to cyclophosphamide, retained their graft, and survived. Follow-up intervals have ranged from 2 months to almost 15 yr for our patient.

It is difficult to calculate the incidence of recurrent WG after transplantation, because neither UNOS (United Network for Organ Sharing) nor USRDS (United States Renal Data System) has data available on the total number of patients with WG who have received kidney grafts. The USRDS 1993 Annual Report, covering 1987 to 1990, shows 318 patients with ESRD due to WG. Of these, 9.4% or 30 patients were transplanted in the first year after ESRD. Reviews by Chandran et al. (19) in 1982 and Kuross et al. (20) in 1981 show a total of 18 patients transplanted at that time, with two episodes of recurrent WG after transplantation.

On the basis of our review, the treatment regimen for such patients must be tailored to their disease activity. First, those patients with inactive disease who are ANCA negative may be treated with a normal posttransplant immunosuppressive regimen. Second, cyclophosphamide and high-dose prednisone are indicated to treat recurrent WG after kidney transplantation, and we recommend continuation of cyclophosphamide until the ANCA reverts to negative. Finally, cyclophosphamide should be considered as a permanent addition to the immunosuppressive regimen in those patients who have persistently positive ANCA or other evidence of active disease.

**SUMMARY AND CONCLUSIONS**

WG is an unusual necrotizing vasculitis affecting the respiratory tract and kidneys. Many patients are

<table>
<thead>
<tr>
<th>Author et al. (Ref. No.)</th>
<th>Age (yr)/Sex</th>
<th>Procedure</th>
<th>Treatment*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronco et al. (5)</td>
<td>49/M</td>
<td>Resection</td>
<td>CP, P</td>
<td>Well at 1 yr</td>
</tr>
<tr>
<td>Scully (6)</td>
<td>60/F</td>
<td>Transureter ureterostomy</td>
<td>CP, P</td>
<td>Well at 16 months</td>
</tr>
<tr>
<td>Metselaar et al. (7)</td>
<td>50/M</td>
<td>Resection, ureterolysis</td>
<td>CP, P</td>
<td>HD* for 4 months well off HD</td>
</tr>
<tr>
<td>Adelizzi et al. (8)</td>
<td>30/M</td>
<td>Resection, ureterolysis</td>
<td>CP, P</td>
<td>Well at 3 yr</td>
</tr>
<tr>
<td>This Report</td>
<td>29/F</td>
<td>Ureteral resection</td>
<td>CP, P</td>
<td>Well at 15 yr</td>
</tr>
</tbody>
</table>

* CP, cyclophosphamide; P, prednisone.
* HD, hemodialysis.
Recurrent Wegener's granulomatosis after kidney transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (yr)/Sex</th>
<th>Original Symptoms</th>
<th>Original Treatment</th>
<th>Recurrent on Dialysis</th>
<th>Years After Tx to Recurrence</th>
<th>Post-Tx Immunosuppression</th>
<th>Location of Recurrence</th>
<th>Treatment of Recurrence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salaman (9)</td>
<td>31/M</td>
<td>Kidney</td>
<td>CP</td>
<td>Yes—lung at 2 yr</td>
<td>3 yr</td>
<td>Aza, Pred</td>
<td>Lung</td>
<td>CP, Pred</td>
<td>Well at 2 months</td>
</tr>
<tr>
<td>Steinman et al. (10)</td>
<td>32/M</td>
<td>Sinus arthralgia, neuralgia, kidney</td>
<td>CP, Pred</td>
<td>None at 1 yr</td>
<td>45 months</td>
<td>Aza, Pred</td>
<td>Sinus, nasal</td>
<td>CP, Pred</td>
<td>Well at 10 months</td>
</tr>
<tr>
<td>Curtis et al. (11)</td>
<td>26/M</td>
<td>Skin, sinus, kidney</td>
<td>None</td>
<td>None at 2 yr</td>
<td>1) 6 months; 2) 2.5 yr</td>
<td>Aza, Pred</td>
<td>1) Lung; 2) Kidney Tx</td>
<td>1) Aza, Pred; 2) CP</td>
<td>Graft failure return to HD</td>
</tr>
<tr>
<td>Lazarovits et al. (12)</td>
<td>10/M</td>
<td>Skin, kidney</td>
<td>Aza, Pred</td>
<td>None at 1 yr</td>
<td>4 months</td>
<td>CSA, Pred</td>
<td>Lung, nasal, oral</td>
<td>CP, Pred</td>
<td>Well at 24 months</td>
</tr>
<tr>
<td>Oberhuber et al. (13)</td>
<td>34/F</td>
<td>Lung, sinus, kidney</td>
<td>CP, Aza Pred</td>
<td>None at 2 yr</td>
<td>31 days</td>
<td>CSA, Pred</td>
<td>Lung, kidney</td>
<td>CP, Pred</td>
<td>Well at 7 months</td>
</tr>
<tr>
<td>Anusholt and Ahiborn (14)</td>
<td>37/M</td>
<td>Sinus, lung</td>
<td>Aza, Pred</td>
<td>None at 6 months</td>
<td>12 months</td>
<td>CSA, Pred</td>
<td>Respiratory arthralgia</td>
<td>CP, Pred; CSA</td>
<td>None; TxNx at 34 days</td>
</tr>
<tr>
<td>Toussaint et al. (16)</td>
<td>33/F</td>
<td>Kidney, lung</td>
<td>Pred</td>
<td>Yes, 9 months arthralgia</td>
<td>15 days</td>
<td>CSA, Pred Aza</td>
<td>Kidney</td>
<td>CP, Pred; CSA</td>
<td>Return to HD; dead at 34 months</td>
</tr>
<tr>
<td>Clarke et al. (16)</td>
<td>38/M</td>
<td>Arthralgia</td>
<td>Aza, Pred</td>
<td>Yes, lung</td>
<td>12 months</td>
<td>CSA, Pred</td>
<td>Lung, sinus</td>
<td>CP, Pred</td>
<td></td>
</tr>
<tr>
<td>Lowance et al. (17)</td>
<td>23/M</td>
<td>Kidney</td>
<td>None</td>
<td>None at 3 yr</td>
<td>15 days</td>
<td>CSA, Pred</td>
<td>Kidney</td>
<td>CP, Pred</td>
<td></td>
</tr>
<tr>
<td>This report</td>
<td>25/F</td>
<td>Nasal, ear, kidney</td>
<td>CP, Pred</td>
<td>None at 10 months</td>
<td>4 months</td>
<td>Aza, Pred</td>
<td>Lung, ureter</td>
<td>CP, Pred</td>
<td></td>
</tr>
</tbody>
</table>

*a* CP, cyclophosphamide; Pred, prednisone; Aza, azathioprine.

*b* Tx, transplant; CSA, cyclosporine.

*c* HD, hemodialysis.

*d* TxNx, transplant nephrectomy.
surviving long term after remissions induced by cytoxic therapy, and those with ESRD do undergo kidney transplantation. The USRDS report for 1987 to 1990 shows that WG is the diagnosis in 0.2% of patients with ESRD. Since the advent of ANCA serologic testing, more cases may be detected in patients who otherwise would have been categorized as having an unknown glomerulonephritis. Most practicing nephrologists will encounter patients with WG. Nephrologists who manage patients after kidney transplantation need to be aware of the possibility of recurrent WG and how best to manage such recurrence. The 10 patients with recurrent WG after kidney transplant represent a significant minority of these patients. Cyclophosphamide and prednisone remain the most effective therapy for WG, even after transplantation.

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REFERENCES