Acute Renal Failure Due to Lymphomatous Infiltration of the Kidneys

GREGORIO T. OBRADOR, BARBARA PRICE, YVONNE O’MEARA, and DAVID J. SALANT
Renal Section, Department of Medicine, Boston University Medical Center, Boston, Massachusetts.

Abstract. Acute renal failure (ARF) is an unusual manifestation of lymphomatous infiltration of the kidneys. In this article, a patient whose initial presentation of lymphoma was the sudden onset of painless hematuria and ARF is described. The absence of other causes of ARF, together with massively enlarged unobstructed kidneys on renal ultrasonography, strongly suggested an infiltrative process. Renal biopsy established the diagnosis of non-Hodgkin’s lymphoma. Pulse steroid therapy was associated with rapid improvement of renal function and kidney size, but a moderate degree of tumor lysis syndrome ensued. Further recovery followed with chemotherapy. Whereas widespread infiltration of the kidneys is present in almost one third of patients with lymphoma at autopsy, this rarely causes clinical symptoms. Nevertheless, because it often responds to therapy, lymphomatous infiltration should be suspected in any patient presenting with unexplained ARF and enlarged kidneys, especially in the setting of widespread lymphoma. (J Am Soc Nephrol 8: 1348–1354, 1997)

Lymphomatous infiltration of the kidneys (LIK) has been reported in one third of patients with diffuse lymphoma at autopsy (1). Although renal involvement is not uncommon, only a few cases of renal failure secondary to diffuse bilateral parenchymal infiltration have been reported in the literature, and in only a minority of these was renal failure the initial manifestation of lymphoma (1–5). Recognition of this cause of acute renal failure (ARF) is important because it often responds to chemotherapy. We report the case of a patient who presented with ARF secondary to massive LIK, in whom chemotherapy effected a rapid improvement in renal function and reduction in kidney size. Gross hematuria from hemorrhagic necrosis of the kidney, and tumor lysis syndrome from steroid-induced lympholysis were additional features of interest in this case. The clinical manifestations, diagnosis, and management of this cause of renal failure are discussed.

Case Presentation
The patient was a 47-year-old white male who developed painful gross hematuria and hesitancy four days prior to hospital admission. The painful hematuria improved over the next two days with “cystitis medication,” but the urine remained dark brown. Laboratory tests done by his primary physician revealed a BUN level of 90 mg/dl and a serum creatinine concentration of 6.1 mg/dl, and the patient was referred to our institution for further evaluation.

The patient had not received regular medical attention until three months prior to admission, when therapy for moderate hypertension was initiated. His baseline creatinine concentration at that time was 1.6 mg/dl. His past history was significant for morbid obesity and a two-pack-a-day history of cigarette use for many years. There was no history of exposure to toxins or use of nonprescription or illicit drugs. His only complaint was of mild fatigue for two months prior to presentation.

Physical examination on admission revealed morbid obesity. His blood pressure was 156/80, and an irregular pulse rate of 128 beats/minute and respiratory rate of 24 breaths/minute were recorded. His temperature was 36.7°C, and there were no other abnormal findings. In particular, there was no lymphadenopathy, and the liver and spleen were not palpable. An electrocardiogram revealed rapid atrial fibrillation that was subsequently controlled with appropriate therapy. The following laboratory values were obtained: BUN, 92 mg/dl; creatinine, 7.4 mg/dl; sodium, 142 meq/liter; potassium, 6.1 meq/liter; chloride, 106 meq/liter; bicarbonate, 24 meq/liter; calcium, 12.7 mg/dl; phosphorus, 6.7 mg/dl; albumin, 3.9 mg/dl; total protein, 7.1 mg/dl; uric acid, 11.2 mg/dl; lactate dehydrogenase, 854 mg/dl; and total bilirubin, 0.4 mg/dl. His hematocrit value was 24%. The white blood cell count was 9500 cells/mm³ with a normal differential count, except for monocytes. The platelet count was 261,000/mm³. There were no schistocytes in the peripheral smear. The erythrocyte sedimentation rate was 150 mm/h. Serum protein electrophoresis showed elevation of the alpha 2 fraction.

Urinalysis revealed a specific gravity of 1.010, pH of 5.0, 2+ protein, and 3+ blood on dipstick testing. Microscopic examination of the spun urine revealed numerous red blood cells but no casts. Renal ultrasound showed massively enlarged hypoechoic kidneys that measured 24 and 25 cm (right and left) in the longitudinal axis (Figure 1). A renal biopsy was performed within 36 h of presentation. All cores revealed extensive infiltration of lymphoid cells compressing relatively well-preserved renal structures (Figure 2). One core contained...
necrotic, hemorrhagic tissue. Immunoperoxidase studies demonstrated positive staining of the neoplastic cells for leukocyte common antigen (CD 45) and the B cell antigen L-26. These results were consistent with non-Hodgkin’s lymphoma (NHL) of the B cell type. Computed tomographic (CT) scanning of the chest and abdomen disclosed peritracheal, mediastinal, and retroperitoneal lymphadenopathy. On bone marrow biopsy, there was diffuse infiltration with large lymphoid cells comprising 20% of cellularity consistent with involvement by high-grade NHL.

The hospital course is summarized in Table 1. The BUN and creatinine levels continued to rise, with peak levels of 117 mg/dl and 8.6 mg/dl, respectively, on the third hospital day. This occurred despite vigorous administration of intravenous fluids for hypercalcemia and a fall of the serum calcium concentration from 12.7 to 11.4 mg/dl. On the second hospital day, pulse steroid therapy (1 g of methylprednisolone intravenously daily for three doses) was commenced. Within 48 h, the serum creatinine concentration fell to 7.7 mg/dl. Despite early initiation of allopurinol (300 mg/d), the patient developed a moderate degree of tumor lysis syndrome (Table 1). A repeat ultrasound done 1 wk after initiation of the steroid pulses showed a dramatic reduction in renal size, with right and left kidneys measuring 16 and 19 cm, respectively (Figure 1). On the 11th hospital day, the serum creatinine concentration had fallen to 3.4 mg/dl and chemotherapy with CHOP (dexamethasone, 20 mg; adriamycin, 50 mg/m²; vincristine, 2 mg; cyclophosphamide, 750 mg/m²; and prednisone, 200 mg on days 2 through 5) was instituted. Renal function continued to improve. At the time of discharge from the hospital on day 15, the BUN and creatinine levels were 44 mg/dl and 2.7 mg/dl, respectively.

Discussion
This case illustrates several interesting points. The patient presented with gross hematuria that was most likely the result of hemorrhagic necrosis of the kidney. This was accompanied by the uncommon occurrence of ARF associated with LIK. The renal failure was rapidly reversed with high-dose steroid therapy. The lympholytic effects of high-dose steroids induced a moderate tumor lysis syndrome, but this did not further impair renal function.

Incidence and Clinical Presentation
The kidney is the most common extranodal site for metastatic lymphoma (1). The involvement is typically diffuse, bilateral (75% of the cases) and symmetrical and is similar in both Hodgkin’s lymphoma and (NHL), although it occurs more
Figure 2. Photomicrograph of kidney biopsy showing diffuse lymphocytic infiltration. Note the compression and separation of renal tubules (arrows) by the monomorphic round cell infiltrate.

Table 1. Laboratory values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 3&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Day 4</th>
<th>Day 11&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dl)</td>
<td>112</td>
<td>117</td>
<td>126</td>
<td>66</td>
<td>44</td>
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<tr>
<td>Creatinine (mg/dl)</td>
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<td>8.6</td>
<td>7.7</td>
<td>3.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
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<td>11.4</td>
<td>11.4</td>
<td>8.5</td>
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<td>11.1</td>
<td>10.2</td>
<td>4.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>11.2</td>
<td>17.7</td>
<td>6.4</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Potassium (mg/dl)</td>
<td>6</td>
<td>6</td>
<td>4.8</td>
<td>4.3</td>
<td>4.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Daily steroid pulse therapy was started.

<sup>b</sup> Chemotherapy with CHOP (see text) was started.

often in the latter. Primary renal lymphoma without evidence of extrarenal spread has also been reported (6–8). The existence of this entity, however, has been questioned because the kidneys do not normally contain lymphoid tissue (9). Renal involvement in patients with diffuse lymphoma has been reported in 6% to 60% of cases at autopsy (10). In the largest series, renal parenchymal involvement was identified in 34% of 696 autopsy cases. Interestingly, of the 142 patients for whom antemortem clinical data was available, lymphomatous infiltration was recognized in only 14% prior to death (1). In contrast, the reported incidence of renal involvement by lymphoma has ranged between 2.7% and 6%, based on reviews of CT scans (11). In patients with newly diagnosed NHL, radiological involvement of the genitourinary tract has been reported in as many as 10% of cases (12). The generally higher frequency of LIK found in autopsy studies reflects the fact that renal involvement is very often clinically silent and that it occurs late in the course of the disease, usually after the diagnosis has been established.

Most patients with LIK have no clinical evidence of renal involvement. When present, renal manifestations are nonspecific and may include flank pain, hematuria, abdominal distension, or a palpable mass. Hypertension, presumably resulting from renal ischemia from compression by the tumor, may also be found. Urinalysis usually reveals mild proteinuria, few red and white blood cells, and occasional hyaline and granular
casts (13–15). Extrarenal symptoms and signs pointing toward lymphoma are frequently present in these patients.

ARF due to LIK is uncommon, and it is rarely the initial manifestation of the lymphoma (2,3,7,13). Although parenchymal lymphomatous infiltration of the kidneys was documented in one third of the 696 autopsy cases reported by Richmond et al, uremic death was attributable to this cause in only five (0.5%) (1). In another study of 49 patients seen between 1949 and 1964, seven (14%) died of uremia. Of the 26 patients autopsied (including five of the seven uremic deaths), 11 (42.3%) had diffuse parenchymal infiltration of the kidneys. In only one case was uremia attributed to massive renal infiltration by lymphoma (14). Table 2 summarizes the incidence and clinical features of LIK.

**Differential Diagnosis**

The clinical picture of hematuria, acute renal failure, hypercalcemia, and massively enlarged kidneys in our patient was suggestive of a renal infiltrative process, most likely a lymphoma. ARF secondary to LIK, however, is a diagnosis of exclusion because kidneys may be massively infiltrated and still maintain relatively normal function. Only rapid reversibility of the renal failure with appropriate chemotherapy can convincingly establish this diagnosis (10).

Table 3 lists the causes of renal failure associated with lymphoma. Retroperitoneal bilateral ureteral obstruction due to compression, invasion, or retroperitoneal fibrosis is probably the most common cause (10). In the autopsy series by Richmond et al, 10% of 696 patients had hydronephrosis, and as many as 4% had evidence of bilateral ureteral obstruction (1). Hypercalcemia, which is most often due to increased calcitriol production (16), is another common cause and/or contributing factor for ARF in this setting. Both volume depletion and renal vasoconstriction may contribute to the renal dysfunction observed with hypercalcemia.

In our patient, obstructive nephropathy was promptly excluded by ultrasonography. Hypercalcemic ARF was unlikely because renal function did not recover, despite substantial improvement in the serum calcium with intravenous fluids. The absence of extreme hyperuricemia (serum uric acid level of greater than 20 mg/dl), oliguria, and uric acid crystals in the urinary sediment argued against acute urate nephropathy. Compression of the renal arteries by lymphoma was ruled out by the absence of severe hypertension, and there were no signs suggestive of rupture of the renal pelvis or ureter, such as ascites or anuria. The presence of only mild proteinuria argued against a glomerular disease, and the renal biopsy did not show the typical glomerular lesions associated with lymphoma (17). In addition, serum protein electrophoresis did not reveal monoclonal gammopathy, and there were no light chains on renal biopsy. Both the massively enlarged kidneys and the rapid improvement of renal function and kidney size with steroid therapy strongly pointed toward the diagnosis of renal failure due to LIK.

The antemortem diagnosis of lymphomatous kidney disease has been greatly aided by the use of CT scanning and ultrasound. Early on, the kidneys may appear to be normal radiologically because the malignant cell masses are well-contained...
in the interstitium, displacing the normal parenchyma but not yet large enough to grossly distort the normal contours of the kidneys. As the malignant cells multiply, ultrasound may reveal hypoechoic masses within the kidney, and a CT scan may show tissue irregularities because lymphomatous infiltrates do not enhance as well as normal kidney tissue with contrast medium (18). The kidneys enlarge with further expansion of tumor masses, and CT scan may show multiple bilateral nodules, diffuse infiltration, and extension to perinephric tissues, ureters, and vasculature. Renal infiltration is almost invariably accompanied by retroperitoneal lymphadenopathy, and it may be difficult to distinguish the renal outline. Angiography is rarely indicated but, when performed, usually reveals hypovascular tissue with evidence of neovascularization and an abnormal, distorted nephrogram (19).

Although the presence of bilateral renal enlargement with nonenhancing nodules or masses of variable size in the renal cortex on CT scan is suggestive of LIK, these findings are not pathognomonic (20). The radiological differential diagnosis of bilateral renal masses includes renal cell carcinoma, multiple abscesses, renal sarcoma, and metastatic solid tumors. There are reports of patients who presented with solitary rather than bilateral renal masses and no evidence of extrarenal spread, in whom lymphoma was misdiagnosed as renal cell carcinoma or other primary renal tumor (6,21). In such cases, kidney biopsy or frozen section is the only way to establish the correct diagnosis.

Tissue diagnosis is usually made by lymph node or bone marrow biopsy in most patients with widespread lymphoma and renal involvement. A kidney biopsy is indicated in those patients in whom these tissues fail to confirm the diagnosis, as well as in those patients in whom tissue sources are not easily accessible. Although the diagnosis could have been made by bone marrow biopsy in our patient, it was believed that kidney biopsy was the most expeditious and direct way to determine the cause of the ARF and define the nature of the infiltrative process. Indeed, the kidney biopsy not only established the diagnosis but also provided valuable information regarding the immunophenotype of the lymphoma and allowed the prompt initiation of therapy. It should be emphasized that tissue for diagnosis should ideally be obtained before therapy is initiated, because chemotherapy—and, even more so, radiotherapy—can grossly distort the lymphoid architecture and preclude a precise histologic diagnosis (10). This is important because knowledge of the immunophenotype of the lymphoma may influence the choice of therapy.

**Pathogenesis**

The mechanism by which lymphomatous infiltration causes renal failure is not known. It has been postulated that dense tumor infiltration of kidney parenchyma may cause compression of the tubular lumen, producing intrarenal obstruction. Histologically, the tubules are indeed compressed and the epithelium is flattened, but the tubular basement membrane is intact (5). Tubular atrophy and necrosis have also been described and appear to recover after treatment (3).

Clinical-pathological correlations have shown that renal infiltration and acute renal failure are more often associated with NHL than Hodgkin's lymphoma (1,5). Moreover, the majority of patients with LIK have high-grade NHL. This is in accordance with the well-established fact that high-grade lymphomas are more aggressive and show frequent extranodal involvement (7).

**Treatment**

Response of renal failure associated with LIK to chemotherapy and/or radiotherapy is generally good. In the series by Glicklich et al., 14 patients were treated with various chemotherapeutic regimens. Six of the 14 also received radiation limited to the kidneys. Three other patients were treated only with kidney irradiation. With these various therapeutic modalities, 11 patients achieved a serum creatinine concentration of less than 2 mg/dl after therapy. The patients whose serum creatinine levels remained greater than 3.0 mg/dl after initial treatment survived for shorter periods of time than those with better renal function. Improvement of renal function was often dramatic, with serum creatinine concentration returning to normal 1 to 4 wk after institution of therapy. The decrease in kidney size to normal paralleled the improvement in renal function. Renal function improved in all three patients who received only radiation to the kidneys. The majority of patients died of progressive lymphoma within 9 mo of presentation with renal insufficiency, however, with only two patients surviving at least 2 yr despite improvement of renal function after chemotherapy or radiotherapy. Survival beyond 4 mo occurred almost exclusively in patients treated with intensive combination chemotherapy (5).

Our patient's renal failure responded dramatically to treatment, in keeping with the results of the above series and other reports (2–4,13). High-dose steroid pulse therapy was remarkably effective in reducing tumor bulk and reversing the acute renal failure while the results of immunophenotyping to initiate specific chemotherapy were awaited. We have encountered two similar case subjects who also had a remarkable renal response to pulse steroid therapy.

A possible complication of aggressive chemotherapy is tumor lysis syndrome. This syndrome comprises a group of metabolic complications including hyperphosphatemia, hypercalcemia (due to precipitation of calcium phosphate), hyperuricemia, hyperkalemia, and ARF. It typically occurs after treatment of rapidly growing tumors (i.e., leukemias and lymphomas). Appropriate hydration and prompt initiation of allopurinol for hyperuricemia, as well as use of phosphate binders for hyperphosphatemia, can reduce the complications associated with this syndrome. Inadequate management may result in further renal impairment due to uric acid and/or calcium phosphate precipitation (10). As shown in Table 1, our patient had biochemical evidence of tumor lysis syndrome of a moderate degree. Appropriate management with hydration and allopurinol prevented further deterioration of renal function. Table 4 summarizes the pathophysiology and treatment of ARF due to LIK.
Table 4. Summary of pathogenesis and treatment of acute renal failure due to lymphomatous infiltration of the kidneys

Pathogenesis
- the mechanism of acute renal failure due to lymphomatous infiltration of the kidneys is unknown
- infiltrate may compress tubules and cause intrarenal obstruction
- reversible acute tubular necrosis (ATN) has been described

Treatment
- rapid improvement with chemo- and/or radiotherapy is seen in most patients
- creatinine level usually returns to normal 1 to 4 wk after therapy is initiated
- decrease in kidney size parallels the improvement in renal function
- hydration and allopurinol are prescribed to protect against the effects of tumor lysis

Prognosis
- patient survival is poor despite recovery of renal function

Subsequent Course
The patient was readmitted to the hospital with urosepsis complicated by adult respiratory distress syndrome 1 wk after discharge. Despite an initial deterioration of renal function as a result of superimposed acute tubular necrosis, he recovered from this complication, and his serum creatinine concentration at discharge was 1.7 mg/dl. He was last seen 5 mo later when he presented with spinal cord compression due to lymphoma, for which he received radiation and steroid therapy. His serum creatinine level usually returns to normal 1 to 4 wk after therapy is initiated. Despite an initial deterioration of renal function as a result of superimposed acute tubular necrosis, he recovered from this complication, and his serum creatinine concentration at that time was still in the 1.8 to 2.0 mg/dl range. The hypertension continued to be easily controlled with verapamil.

Conclusion
Although renal failure as a result of lymphomatous parenchymal infiltration is uncommon, it should be suspected in any patient presenting with unexplained ARF and enlarged kidneys, especially if the patient is known to have lymphoma. After other causes of renal failure have been reasonably excluded, radiographic demonstration of enlarged kidneys in the absence of obstruction is highly suggestive of this diagnosis. Prompt initiation of therapy often results in rapid improvement of renal function.

Acknowledgments
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References
The Training Program in Nephrology at Boston University

The Renal Section at Boston University has been training fellows for more than 30 years. The Training Program is directed by Dr. David Salant, a graduate of the program. Previous directors include Drs. Arnold Relman, Charles Burnett, Jacob Lemann, and Norman G. Levinsky. The Section has trained more than 100 nephrologists, most of whom have gone on to academic careers as members and leaders of renal divisions and departments of medicine throughout the United States, Canada, and several other countries. Approximately 75% of graduates since 1967 have entered academia. Other graduates have become prominent practicing nephrologists, responsible for regional dialysis units and clinical nephrology programs in university-affiliated teaching hospitals.

The Renal Section offers comprehensive clinical and research training supervised by a full-time staff of 15 nephrologists and medical scientists, as well as several associate research training faculty. The size of the staff permits broad coverage of the various clinical and research areas of nephrology. It also provides intensive supervision of fellows during both clinical and research training. Most fellows are physicians who have completed their training as the basis for a career in academic nephrology. For these individuals, a comprehensive fellowship program includes one year of clinical training in nephrology, usually—but not necessarily—taken first, and two or more years of research training. Other physician-trainees, anticipating a career in clinical nephrology, take the year of training in clinical nephrology followed by a year or more of training in clinical investigation or hypertension. A broad clinical experience is facilitated by rotations through Boston Medical Center, the Boston VA Medical Center, and the Gambro Dialysis Center at the Boston University Medical Center. Training positions are also open to Ph.D. medical scientists who wish to receive postdoctoral fellowship training in aspects of physiology, molecular and cell biology, immunology, and health services research related to the kidney or its diseases. In addition, close ties have been established with basic scientists in other departments, which affords fellows the opportunity of training in molecular biology and basic immunology. Research activities are supported by several research grants and an institutional training grant from the National Institutes of Health.

Erratum

The recent article by the Modification of Diet in Renal Disease (MDRD) Study Group, “Effects of Diet and Antihypertensive Therapy on Creatinine Clearance and Serum Creatinine Concentration in the Modification of Diet in Renal Disease Study” (J Am Soc Nephrol 7: 556-566) stated incorrectly that “serum and urine creatinine concentrations were measured by an alkaline picrate assay with Lloyd’s reagent and a kinetic alkaline picrate assay.” These measurements were not performed using Lloyd’s reagent. The normal range for serum creatinine, using the kinetic alkaline picrate method (Beckman ASTRA 8, Beckman, Fullerton, CA), is 0.7 to 1.4 mg/dl.