PathoLogic

A Young Man with HIV Infection and Acute Renal Failure

Ursula C. Brewster, MD
Mark A. Perazella, MD, FACP

CASE PRESENTATION

A 34-year-old man with a history of HIV infection presented to the hospital complaining of weakness, anorexia, and decreased urine output. His past history also included pulmonary infection with *Pneumocystis carinii*, systemic *Mycobacterium avium intracellulare* infection, and candida esophagitis. Medications included lamivudine 150 mg twice daily, lopinavir/ritonavir 400/100 mg twice daily, tenofovir 300 mg once daily, oxycodone 60 mg twice daily, fluconazole 150 mg per week, and prevacid 30 mg once daily. The patient was on a stable regimen of these drugs for at least 10 months. Celecoxib 200 mg twice daily was added 3 weeks prior to admission for an acute back injury. His serum creatinine concentration measured 2 months prior to this admission (5 weeks prior to celecoxib therapy) was 1.3 mg/dL, with a calculated creatinine clearance of 68 mL/min.

Physical examination revealed a thin young man with a temperature of 98.6°F (37°C), blood pressure of 115/70 mm Hg, and a pulse of 85 bpm with no orthostatic changes. Head and neck were unremarkable, and jugular venous pulsations were present at 30 degrees. The lungs were clear to auscultation, and the heart had normal sounds without murmur, rub, or gallop. Abdominal examination was benign, and there was no lower extremity edema. No rash, petechiae, or purpura were present on the skin. Both cervical and inguinal lymphadenopathy were present.

Laboratory results were notable for the following: serum sodium, 132 mEq/L; potassium, 4.9 mEq/L; chloride, 96 mEq/L; bicarbonate, 16 mEq/L; blood urea nitrogen, 46 mg/dL; serum creatinine, 3.3 mg/dL. Complete blood count revealed: leukocyte count, 8.6 × 10^3/mm^3 with 69% polymorphonucleocytes, 24% lymphocytes, 4% monocytes, and 3% eosinophils; hemoglobin, 9.6 g/dL; hematocrit, 29%; and platelet count, 165 × 10^3/mm^3. The most recent CD4 count was 250 cells/m^3 with an undetectable viral load. Results of liver function testing were unremarkable. Creatine phosphokinase level was within normal limits. Urinalysis showed 2+ protein on dipstick. The urine sediment contained a few granular casts, renal tubular epithelial cells, and 3 to 5 erythrocytes and 4 to 6 leukocytes per high power field. A spot urine test for protein and creatinine revealed a ratio consistent with a protein output of 1.3 g/day. The renal ultrasound revealed large (≥ 14 cm) kidneys with increased echogenicity. There was no evidence of hydronephrosis, renal masses, or stones.

The patient received intravenous normal saline solution (2 L) to expand the intravascular volume and treat any potential subtle volume depletion. Celecoxib was discontinued and the antiretroviral medications were held. Despite these interventions, renal function worsened over the next 3 days, with the creatinine level increasing to 5.9 mg/dL. At this time, a renal biopsy was performed to identify the cause of acute renal failure. The biopsy demonstrated a diffuse interstitial infiltrate, predominantly lymphocytic, with marked tubulitis and interstitial edema (**Figure 1**). A few scattered eosinophils also were present (**Figure 2**). The glomeruli and vessels were unremarkable. Electron microscopy demonstrated normal glomeruli without evidence of foot process effacement, electron dense deposits, or glomerulosclerosis. Immunofluorescence microscopy was negative for immune staining.

Dr. Brewster is a clinical instructor, and Dr. Perazella is an associate professor of medicine; both are in the Section of Nephrology, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT.

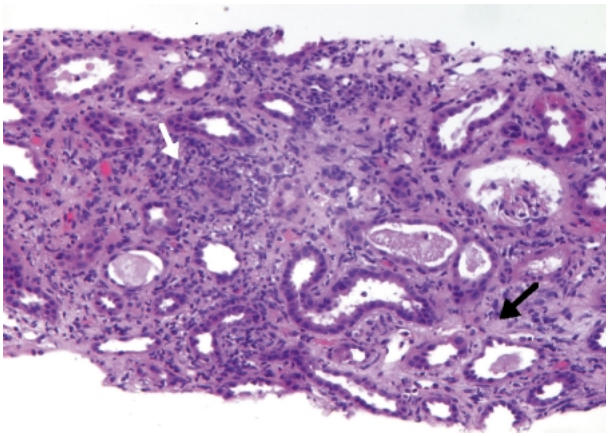

Figure 1. Low power light microscopy view of the case patient's kidney showing a severe predominantly lymphocytic infiltrate (*white arrow*) and interstitial edema (*black arrow*). Hemotoxylin-eosin stain, 20×.

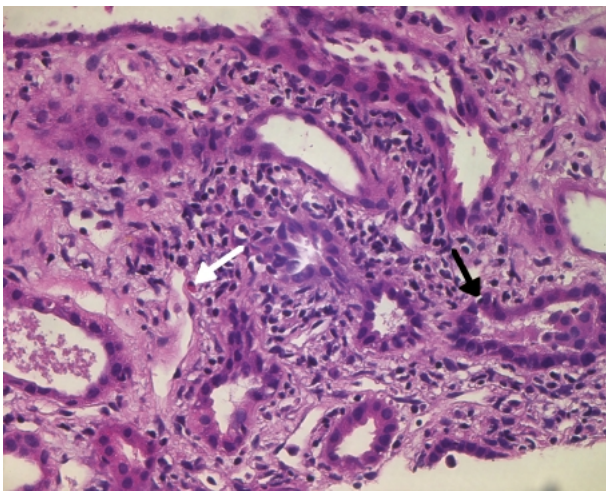

Figure 2. High power light microscopy view of kidney showing rare eosinophils (*white arrow*), tubulitis (*black arrow*), and interstitial infiltrate. Hemotoxylin-eosin stain, 40×.

1. What is the most likely cause of the patient's acute renal failure?

(A) Acute renal failure from HIV-associated nephropathy
(B) Acute tubular necrosis from tenofovir
(C) Acute tubulointerstitial nephritis (ATIN) from celecoxib
(D) Crystal nephropathy associated with lopinavir/ritonavir
(E) Hemodynamic renal failure from celecoxib

2. What is the best approach to therapy in this patient?

(A) Administer corticosteroids to increase resolution of ATIN
(B) Alkalinize the urine with intravenous fluids containing sodium bicarbonate to reduce injury from myoglobinuria
(C) Continue intravenous fluids and administer furosemide to wash out obstructing crystals in the distal nephron
(D) Continue intravenous normal saline solution to correct intravascular volume depletion
(E) Give intravenous dopamine to increase blood flow and glomerular filtration rate

ANSWERS

The correct answers are (C) ATIN from celecoxib; and (A) administer corticosteroids to increase resolution of ATIN.

OUTCOME OF CASE

The biopsy findings were consistent with ATIN. The patient was treated with 10 mg of intravenous decadron (1 dose) followed by oral prednisone 60 mg per day for 2 weeks. Over the next 3 weeks, the serum creatinine concentration declined from 5.9 mg/dL to 1.2 mg/dL. The corticosteroids were rapidly tapered off over the next week. Six months later, the patient's kidney function was stable with a creatinine concentration of 1.1 mg/dL.

The selective cyclooxygenase-2 (COX-2) inhibitors have been described to cause renal syndromes that parallel those of the traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). To date, acute renal failure, hyperkalemia (type 4 renal tubular acidosis), hyponatremia, edema, and hypertension have been reported in the literature in association with COX-2 inhibitors.[1–3] A subset of patients being treated with NSAIDs are at risk for hemodynamic acute renal failure because they depend on vasodilatory prostaglandins (PGE_2, PGI_2) to maintain renal blood flow and glomerular filtration. Examples of such patients include those with states of true volume depletion (eg, from vomiting, diarrhea, overdiuresis) and effective volume depletion (eg, from heart failure, cirrhosis, nephrosis), as well as in chronic kidney disease. Prostaglandins act to counteract the vasoconstrictive effects of endogenous substances such as catecholamines, endothelin, and angiotensin II, which are produced in these clinical disease states. Based on this known effect, celecoxib-associated inhibition of vasodilatory prostaglandins was considered as a possible cause of hemodynamic acute renal failure in the case patient. Despite discontinuation of celecoxib and volume repletion with intravenous normal saline, however, renal function

continued to deteriorate. Hemodynamic acute renal failure typically resolves quickly once the offending agent is removed, making this diagnosis unlikely in this patient.

Also on the differential diagnosis of this patient's acute renal failure was tenofovir-associated kidney disease. Tenofovir has been described to cause acute tubular necrosis[4] and Fanconi syndrome.[5] The uptake of tenofovir by the basolateral organic anion transporter in the proximal tubule likely underlies its proclivity to cause toxicity in this cell. In the case patient, the renal biopsy excluded acute tubular necrosis as the cause of acute renal failure in this patient.

The possibility of ATIN resulting from tenofovir was considered but thought to be unlikely. This conclusion was based on the fact that tenofovir had been well tolerated for at least 10 months prior to this event. Furthermore, tenofovir has not been noted in the literature to cause ATIN.

HIV-associated nephropathy is a consideration based on the clinical findings of acute renal failure, proteinuria, and large echogenic kidneys demonstrated on ultrasonography. However, the renal biopsy findings of normal glomeruli exclude the diagnosis of HIV-associated nephropathy in this patient.

The temporal association of administration of celecoxib (3 weeks prior to the presentation with acute renal failure) and the development of ATIN suggests that this selective COX-2 inhibitor was the culprit drug. As with traditional NSAIDs, it appears that ATIN complicates therapy with this new class of drugs. Two cases of ATIN from celecoxib and 2 cases of ATIN from rofecoxib (only 1 biopsy-proven) have been reported in the literature (**Table 1**).[6–9] One of the cases of celecoxib-associated ATIN also had concurrent minimal change disease on the renal biopsy, a finding that also has been seen with traditional NSAIDs.[6]

The mechanism of ATIN associated with selective COX-2 inhibitors is unknown. Because these drugs block cyclooxygenase, arachidonic acid may be shunted into the lipoxygenase pathway, favoring the production of proinflammatory leukotrienes. Production of these prostanoids could then result in the development of ATIN.[10] As celecoxib contains a sulfa group, the possibility of an allergic reaction to this medication as the cause of ATIN needs to be considered. However, the patient did not have an allergy to sulfa-containing medications, making it unlikely that an IgE-mediated reaction caused the ATIN. Nonetheless, it is possible that either humoral- or cell-mediated immune mechanisms may be responsible for ATIN with these drugs. HIV-infected patients appear to develop ATIN from drugs more commonly than the general population.[11] This may reflect a disturbed immune system.

Table 1. Cases of ATIN Associated with the Selective COX-2 Inhibitors

Drug	First Author	Peak SCr	Treatment	Final SCr
Celecoxib	Alper[6]	2.1 mg/dL	Steroids	1.1 mg/dL
Celecoxib	Henao[7]	11.8 mg/dL	Hemodialysis	1.1 mg/dL
Celecoxib	Brewster*	5.9 mg/dL	Steroids	1.2 mg/dL
Rofecoxib	Rocha[8]	8.7 mg/dL	Hemodialysis, steroids	1.4 mg/dL
Rofecoxib	Alim[9]	13.6 mg/dL	Hemodialysis	1.3 mg/dL

ATIN = acute tubulointerstitial nephritis; COX = cyclooxygenase; SCr = serum creatinine concentration.

*Current case.

DIAGNOSIS

The diagnosis of ATIN should be suspected in patients with the appropriate clinical manifestations (**Table 2**) and a history of exposure to a culprit drug.[12,13] Certain laboratory findings, such as peripheral eosinophilia and urinary eosinophils, are suggestive of ATIN but are insufficient to clinch the diagnosis. The absence of any such clinical findings, however, does not eliminate ATIN as a suspect.[14]

Renal ultrasound and computed tomography scanning often reveal enlargement of both kidneys with diffuse hyperechogenicity in the cortex.[15] In one report, renal volume increased to as much as 200% of the original volume.[15] Presumably, this is related to an expansion of the interstitium by edema that is associated with the cellular infiltration. Again, these findings are neither sensitive nor specific for ATIN and may be seen with other infiltrative or proliferative renal lesions. These imaging studies are useful mainly for excluding other etiologies of renal failure, such as urinary obstruction, and documenting the presence of 2 kidneys.

Renal scanning with gallium citrate Ga 67 has been reported as a useful imaging modality to detect ATIN in some patients. Data from small patient series reveal that gallium scan appears to have excellent sensitivity for evaluation of ATIN.[16] In these series, patients with a negative gallium scan did not have evidence of ATIN on kidney biopsy. However, the test is not specific for ATIN, and positive results have been demonstrated in other inflammatory renal conditions such as pyelonephritis, chronic interstitial nephritis, and glomerulonephritis. False-positive results also have been seen in patients without any specific abnormality on renal

Table 2. Clinical and Laboratory Findings in Drug-Induced ATIN

Signs and symptoms
Constitutional symptoms (anorexia, malaise, fever)
Arthralgia, arthritis (rare)
Myalgia, myositis (rare)
Fever
Skin rash
Flank pain, tenderness, palpable flank mass
Serum
Eosinophilia
Anemia
Elevated serum IgE levels
Elevated serum transaminase levels*
Elevated BUN and creatinine
Hyperkalemia, hypokalemia
Hyperchloremic metabolic acidosis
Urine
Proteinuria
Hematuria
Leukocyturia
Eosinophiluria
Renal tubular epithelial cells/ casts
Elevated urine major basic protein level

ATIN = acute tubulointerstitial nephritis.

*In patients with associated drug-induced liver injury.

biopsy. In general, acute tubular necrosis yields a negative gallium scan result. Therefore, the utility of the gallium scan lies mainly in differentiating ATIN from acute tubular necrosis in the patient who is a poor biopsy candidate or refuses renal biopsy. In such a patient, and in patients in whom there is no contraindication to corticosteroid therapy, another reasonable approach would be a trial of corticosteroids. Hence, treatment with corticosteroids may be both diagnostic and therapeutic in some patients with ATIN.

The definitive diagnosis of ATIN can be established only by renal biopsy, and should be performed in any patient in whom the diagnosis is uncertain and in whom there is no contraindication for the procedure.[17] Similarly, renal biopsy is indicated in the patient who has clinical features suggestive of ATIN but fails to show any improvement in renal function with discontinuation of the suspected offending agent. As noted above, in the patient who is a poor biopsy candidate, an empiric trial of corticosteroids may be an acceptable alternative.

PATHOLOGY

Whereas the clinical features associated with drug-induced ATIN are variable, the renal histopathologic lesion is quite constant. The most striking feature on light microscopy is a cellular infiltrate in the peritubular areas of the interstitium, often associated with interstitial edema.[18] The infiltrate shows a predominance of plasma cells and lymphocytes and a variable quantity of macrophages and eosinophils. On occasion, the inflammatory cell may insinuate between the epithelial cells or may be located between the basement membrane and the tubular cell, so-called "tubulitis." Tubulitis may be accompanied by rupture of the tubular basement membrane and leakage of Tamm-Horsfall protein into the interstitium. Rarely, frank granulomas with giant cells have been described. Depending on the duration of drug exposure and renal inflammation, there may be focal or diffuse areas of fibrosis. The tubules may exhibit variable degrees of atrophy associated with degenerative changes and with evidence of regeneration. Hyaline droplets can be seen in the tubular cells, and hyaline casts can be seen in the tubular lumina. Focal and segmental peritubular basement membrane thickening sometimes can be seen. Some authors have noted that the distal tubules appear to be affected more severely than the proximal tubules. This is consistent with the clinical observation of a distal renal acidification defect. In general, there is little or no deposition of immunoglobulins detected by immunofluorescence, although the presence of antitubular basement membrane antibodies as well as IgG in the interstitium has been described in some cases.[12]

Electron microscopy demonstrates swelling of the mitochondrial structures or of the entire tubular cell. In general, the glomeruli and vasculature are spared, but glomerular inflammation and benign arteriolar sclerosis occasionally may be present.

TREATMENT

The mainstay of therapy in drug-induced ATIN is discontinuation of the offending agent.[19] Most patients will recover renal function if the drug is removed promptly. However, the probability of good recovery depends on the duration of renal failure prior to diagnosis of ATIN. Patients with acute renal failure from ATIN who are treated within 2 weeks of onset may recover more renal function (as evidenced by lower serum creatinine concentrations) than patients in whom treatment is delayed for more than 3 weeks.

Data from anecdotal reports and small patient series suggest that corticosteroid therapy may be beneficial in ATIN.[12,17] However, there have been no prospective,

randomized controlled trials that prove corticosteroid efficacy. Overall, there has been no significant difference in the severity of renal failure (defined by peak serum creatinine level) or need for dialytic therapy with corticosteroids. Similarly, most patients recover some degree of renal function whether or not they received corticosteroids, although it appears that a larger number of corticosteroid-treated patients return to their baseline level of renal function.[12,17] In addition, some studies do suggest that corticosteroid therapy shortens the time to renal recovery.[12,17]

A correlation between histologic findings and clinical course of ATIN has been described.[14] Patients with only patchy inflammatory infiltration are more likely to recover renal function than patients with diffuse infiltration. The presence of excess numbers of neutrophils also seems to be an adverse prognostic factor. For many renal diseases, the extent of interstitial fibrosis is predictive of renal outcome. Intuitively, this is also applicable to ATIN, in that patients with diffuse fibrosis on biopsy are less likely to recover renal function, regardless of therapy.

Although there is a lack of controlled data on corticosteroid therapy, a rational approach to the treatment of drug-induced ATIN would be as follows: (1) Consider ATIN in the differential diagnosis of acute renal failure; (2) withdraw the offending agent and observe blood urea nitrogen and serum creatinine levels; (3) if renal function does not improve within approximately 7 days, a renal biopsy should be undertaken if no contraindication exists.

If the duration of acute renal failure is less than 3 weeks, there is minimal fibrosis on biopsy, and there are no contraindications for corticosteroid therapy, prednisone should be started at an initial dose of 1 mg/kg body weight daily. If renal function improves, high-dose corticosteroid therapy is maintained for 2 to 3 weeks, and the dose tapered over the following 3 to 4 weeks. Corticosteroids should be discontinued if no meaningful improvement in renal function is achieved after 3 to 4 weeks of high-dose therapy.

If a contraindication to renal biopsy is present or the patient refuses renal biopsy, either a trial of corticosteroid therapy should be considered if no contraindication exists or a gallium scan can be performed. As above, if no improvement occurs with corticosteroid therapy, this medication should be discontinued and supportive management undertaken. A negative gallium scan mandates continued work-up for another cause of renal insufficiency; a positive scan increases the likelihood of ATIN if other causes of a positive scan are absent.

CONCLUSION

Physicians should be aware that selective COX-2 inhibitors have the potential to cause ATIN, as do traditional NSAIDs. A diagnosis of ATIN should be considered in patients who develop acute renal failure following the ingestion of these drugs. Hemodynamic renal failure from COX-2–associated inhibition of vasodilatory prostaglandins also is a possibility; however, hemodynamic renal failure typically improves within 48 to 72 hours of drug discontinuation. Definitive diagnosis of ATIN requires biopsy; in some cases, however, a trial of corticosteroids and/or a gallium scan may assist in the diagnosis. **HP**

REFERENCES

1. Perazella MA, Eras J. Are selective COX-2 inhibitors nephrotoxic? Am J Kidney Dis 2000;35:937–40.
2. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. Am J Med 2001; 111:64–7.
3. Perazella MA. COX-2 selective inhibitors: analysis of the renal effects. Expert Opin Drug Saf 2002;1:53–64.
4. Coca S, Perazella MA. Rapid communication: acute renal failure associated with tenofovir: evidence of drug-induced nephrotoxicity. Am J Med Sci 2002;324:342–4.
5. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis 2002;40:1331–3.
6. Alper AB Jr, Meleg-Smith S, Krane NK. Nephrotic syndrome and interstitial nephritis associated with celecoxib. Am J Kidney Dis 2002;40:1086–90.
7. Henao J, Hisamuddin I, Nzerue CM, et al. Celecoxib-induced acute interstitial nephritis. Am J Kidney Dis 2002;39:1313–7.
8. Rocha JL, Fernandez-Alonso J. Acute tubulointerstitial nephritis associated with the selective COX-2 enzyme inhibitor, rofecoxib [letter]. Lancet 2001;357:1946–7.
9. Alim N, Peterson L, Zimmerman SW, Updike S. Rofecoxib-induced acute interstitial nephritis [letter]. Am J Kidney Dis 2003;41:720–1.
10. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. Am J Med 1999;106:13S–24S.
11. Perazella MA. Acute renal failure in HIV-infected patients: A brief review of common causes. Am J Med Sci 2000;319:385–91.
12. Ten RM, Torres VE, Milliner DS, et al. Acute interstitial nephritis: immunologic and clinical aspects. Mayo Clin Proc 1988;63:921–30.
13. Revert L, Montoliu J. Acute interstitial nephritis. Semin Nephrol 1988;8:82–8.
14. Laberke HG, Bohle A. Acute interstitial nephritis: correlations between clinical and morphological findings. Clin Nephrol 1980;14:263–73.

 (continued on page 46)