Published in final edited form as:

N Engl J Med. 2010 November 4; 363(19): 1847–1851. doi:10.1056/NEJMcps0904937.

Bitter Pills

Yonatan H. Grad, M.D., Ph.D., Julian L. Seifter, M.D., Bruce D. Levy, M.D., and Joseph Loscalzo, M.D., Ph.D.

Clinical Pathological Conference Series, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School — both in Boston

A 60-year-old man presented to an urgent care clinic with fatigue of 1 month's duration and increasing frequency of urination, nighttime urination, and increasing thirst over the previous week. He had earlier been told that he had prediabetes and was now concerned that his symptoms reflected progression to diabetes mellitus. He was otherwise in his usual state of health. He reported no dysuria, urgency, incomplete bladder emptying, straining to initiate urination, fevers, chills, arthralgias, or rash.

It is reasonable for this patient with prediabetes to be concerned about progression to overt diabetes mellitus. Elevated levels of plasma glucose can lead to an osmotic diuresis when large quantities of filtered glucose exceed the reabsorptive capacity of the renal proximal tubule.

The symptom of urinary frequency should be clarified. Does this patient have frequent voiding of small amounts of urine, which is typical of problems in the lower urinary tract, or polyuria, in which the volume of urine output is large? He reports no symptoms that are characteristic of urinary tract infection or other disorders of the urinary tract. His increased thirst, which suggests increased fluid ingestion, may be physiological (e.g., due to a psychiatric condition, brain lesion, or conditions or medications leading to a dry mouth) or the result of other causes (e.g., due to hyperosmolality or dehydration). Nocturia is consistent with a large urinary volume resulting from any cause and could reflect expansion of intravascular volume with supine posture at night, when volume from the lower extremities is returned to the circulation. Patients with kidney disease may lose the normal ability to concentrate the urine overnight.

The patient's medical history was notable for anxiety, depression, hypercholesterolemia, seasonal allergies, hypogonadism, and gastroesophageal reflux disease. Three months before seeking urgent care, he had an upper respiratory tract infection that was treated with a 5-day course of azithromycin. He had been evaluated in the past year for resting tachycardia;

Copyright © 2010 Massachusetts Medical Society.

Address reprint requests to Dr. Levy at the Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115, or at blevy@partners.org.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

An Interactive Medical Case related to this Clinical Problem-Solving article is available at NEJM.org

No potential conflict of interest relevant to this article was reported.

assessment results included a normal level of thyrotropin, a normal exercise stress test, and an absence of coronary artery disease on cardiac catheterization. His regular medications included full-strength aspirin (taken for its cardioprotective effect), diazepam, venlafaxine, atorvastatin, omeprazole, budesonide, St. John's wort, and testosterone gel. The patient was a community college professor and was married. He did not smoke; he drank two cups of coffee daily and two shots of whisky (also taken because of the patient's belief in its cardioprotective effect) each evening. His mother died at 96 years of age. His father died at 50 years of age from ischemic heart failure and had three siblings with myocardial infarction.

It is important to obtain a complete history of medications and nonprescription remedies, including over-the-counter medications, vitamins, and herbal and other dietary supplements. St. John's wort, for example, can have anticholinergic effects, including tachycardia and dry mouth, which may lead to polydipsia. Ethanol can increase hypotonic urinary losses by suppressing vasopressin. Drinks containing caffeine may also induce a mild diuresis and tachycardia. Atrial tachyarrhythmias may be associated with increased release of natriuretic peptides.

On physical examination, the patient appeared anxious. His temperature was 98.9°F, his pulse 110 beats per minute and regular, and his blood pressure 138/90 mm Hg without postural changes. The results of cardiac, pulmonary, abdominal, prostate, thyroid, and skin examinations were normal. There was no flank tenderness. A guaiac test of a stool specimen was negative. The blood glucose level, as measured with a fingerstick test, was 101 mg per deciliter (5.6 mmol per liter). The sodium level was 140 mmol per liter, potassium 4.4 mmol per liter (17 mg per deciliter), chloride 103 mmol per liter, bicarbonate 27 mmol per liter, blood urea nitrogen 44 mg per deciliter (16 mmol per liter), and creatinine 3.1 mg per deciliter (274 μ mol per liter); 9 months earlier the baseline creatinine level was 1.1 mg per deciliter (97 μ mol per liter). The white-cell count was 10,400 per cubic millimeter, the hematocrit 46.2%, and the platelet count 308,000 per cubic millimeter. Urinalysis revealed a specific gravity of 1.008 and a pH of 7.5; neither glucose nor protein was present, but there was sediment that showed 10 to 15 red cells and 5 to 9 white cells per high-power field, with no squamous epithelial cells and no bacteria.

A normal blood glucose level and the absence of glycosuria indicate that the patient's presenting symptoms are not due to diabetes mellitus. The elevated level of blood urea nitrogen and the elevated creatinine level, in comparison with the earlier creatinine level, indicate recent kidney injury. Diagnostic considerations for a recent onset of renal failure include urinary tract obstruction; tubulointerstitial nephritis; rapidly progressive glomerulonephritis, including postinfectious, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and IgA nephropathy; myeloma cast nephropathy; and microvascular diseases, such as the thrombotic microangiopathies.

The presence of polyuria suggests tubular dysfunction in water reabsorption rather than glomerular disease. Urinary obstruction can cause kidney injury with oliguria, normal urinary volume, or polyuria and should be evaluated by means of renal ultrasonography. Pyuria and hematuria point to an inflammatory process. The urine should be carefully

examined for white-cell casts and red-cell casts, either of which would point to a diagnosis of acute tubulointerstitial nephritis or glomerulonephritis, although failure to identify casts would not rule out intrinsic renal disease. Giemsa staining of a cytospin preparation of urinary sediment shows lymphocytes, plasma cells, and eosinophils in cases of acute tubulointerstitial nephritis. A differential white-cell count in a peripheral-blood specimen would be warranted, since acute tubulointerstitial nephritis is often associated with peripheral eosinophilia.

Urinary tract infection remains a possibility, but that alone would not explain the renal failure. Acute tubulointerstitial nephritis can cause defects in urinary concentration, both polyuria and pyuria, and hematuria. In contrast, acute glomerulonephritis is usually associated with oliguria, concentrated urine, dysmorphic red cells, and red-cell casts in urinary sediment; none of these features are present in this case. Autoimmune processes, such as Sjögren's syndrome, lupus erythematosus, and ANCA-associated renal disease, may be manifested as interstitial disease, glomerular disease, or both. The patient has no history of rash, arthralgias, or pulmonary disease, findings that would suggest systemic vasculitis or lupus erythematosus.

Multiple myeloma is a possibility, and a serum protein electrophoresis should be ordered. Although protein casts in multiple myeloma can cause oliguric renal failure, light-chain deposition in the renal tubules may result in polyuria and renal failure. New-onset renal insufficiency can also be caused by atheroembolic renal disease, which may occur after a cardiac catheterization, but this condition typically develops soon after the procedure; in this patient several months have passed since catheterization. Thrombotic microangiopathy is unlikely in the absence of thrombocytopenia and hemolysis.

The patient had been taking all his medications for many years, with the exception of omeprazole, which he began taking approximately 2 months before presentation, and the short course of azithromycin. He reported taking no over-the-counter or herbal medications other than those reported. Repeat laboratory testing the day after evaluation in urgent care revealed a blood urea nitrogen concentration of 47 mg per deciliter (17 mmol per liter) and a creatinine concentration of 3.6 mg per deciliter (318 μ mol per liter). The automated differential white-cell count showed 77.3% neutrophils, 12.8% lymphocytes, 4.9% eosinophils, 4.4% monocytes, and 0.6% basophils. No casts or eosinophils were observed on evaluation of the urinary sediment. Serum and urine protein electrophoresis showed no M spike. The results of tests for antinuclear antibodies, ANCA, anti-glomerular basement membrane antibodies, and antistreptolysin O were unremarkable. Ultrasonography of the kidneys showed normal-size kidneys without evidence of hydronephrosis.

The finding of normal-size kidneys on ultrasonography is consistent with an acute or subacute process, and the absence of hydronephrosis rules against obstruction. The negative tests for serologic markers help rule out autoimmune diseases, and the normal results on serum and urinary protein electrophoresis rule out multiple myeloma. Thus, the clinical picture at this point is most suggestive of acute tubulointerstitial nephritis. Although fever, rash, eosinophilia, and the presence of eosinophils in the urine are commonly associated with allergic acute tubulointerstitial nephritis, these findings are not universal. Multiple

medications have been associated with the condition, including both azithromycin and omeprazole, to which the patient has recently been exposed. Certain herbal medications have also been linked to acute tubulointerstitial nephritis. Given the continued rise in the patient's creatinine level, it is best to establish a pathological diagnosis by examining a specimen from a percutaneous renal biopsy.

The patient was admitted to the hospital for expedited evaluation. Examination of a renal-biopsy specimen revealed severe acute interstitial nephritis. There was extensive interstitial inflammation with many eosinophils, extensive degenerative changes of the tubular cells, and thin glomerular basement membranes (Fig. 1).

The renal-biopsy specimen reveals edema and lymphocytic infiltrates, confirming the clinical impression of tubulointerstitial nephritis. The presence of eosinophils suggests an allergic cause. The most likely culprit is omeprazole, given its recent introduction and continued use. The pathological finding of thin glomerular basement membranes is not causally related to the acute kidney injury, but it is a common cause of persistent microhematuria.

Management of this patient's condition requires cessation of the medications that might be causing the allergic reaction and consideration of an antiinflammatory regimen. The optimal regimen is uncertain, but with histopathological evidence of progressive renal injury and a severe inflammatory response, a course of glucocorticoids, guided by the response to therapy, is reasonable.

The patient agreed to stop all medications except venlafaxine and aspirin, both of which he considered indispensable. His creatinine level showed improvement after intravenous administration of 1 g of methylprednisolone per day for 3 days. He was discharged with a prescription for prednisone, 1 mg per kilogram of body weight, with a plan to taper the dose over the course of a month. At the time of discharge, his creatinine level was 2.6 mg per deciliter (230 μ mol per liter), down from a peak value of 3.9 mg per deciliter (345 μ mol per liter). Seven days later, the patient presented to the emergency room with syncope and on examination was found to have orthostatic hypotension. While in the emergency room, he had melena. The level of blood urea nitrogen was 59 mg per deciliter (21 mmol per liter), and the creatinine level was 2.0 mg per deciliter (177 μ mol per liter). The white-cell count was 33,000 per cubic millimeter, the hematocrit 41%, and the platelet count 377,000 per cubic millimeter. After intravenous hydration, the blood urea nitrogen level was 72 mg per deciliter (26 mmol per liter), and the creatinine level was 1.6 mg per deciliter (141 μ mol per liter); the hematocrit was 33%. The hematocrit fell to 26% over the next 12 hours, and symptomatic hypotension developed. The patient was transferred to the intensive care unit, where packed red cells were immediately transfused.

The patient now presents with apparent upper gastrointestinal bleeding, for which he was at increased risk, given his use of glucocorticoids and aspirin. The elevated level of blood urea nitrogen probably reflects bleeding in the gastrointestinal tract and the catabolic effect of cortisol. The reduction in his creatinine level after intravenous fluid resuscitation indicates

that his kidney injury on this admission was probably due to a prerenal state associated with volume loss from bleeding rather than worsening of his tubulointerstitial nephritis.

Urgent endoscopy revealed two chronic gastric ulcers with an adherent clot at the ulcer base. Pathological analysis showed erosive gastritis without evidence of dysplasia or infection with *Helicobacter pylori*. Treatment with an H₂-receptor blocker was started, and the patient was discharged in good condition. Follow-up endoscopic examinations confirmed healing of the gastric ulcers. The patient's creatinine level returned to baseline, and over the next 3 years, his renal function was stable, with no recurrence of acute tubulointerstitial nephritis.

COMMENTARY

Tubulointerstitial nephritis is identified as the cause of acute kidney injury in 15 to 27% of patients undergoing diagnostic renal biopsy for such injury.^{1,2} The histologic hallmarks of tubulointerstitial nephritis include an interstitial inflammatory response with edema and tubular injury. The causes include drug-induced allergic reactions, infection, autoimmune inflammation (e.g., systemic lupus erythematosus and Sjögren's syndrome), and the syndrome of tubulointerstitial nephritis and uveitis. Medications account for about 70% of cases,¹ and proton-pump inhibitors are increasingly implicated.³

The classic triad of fever, peripheral eosinophilia, and rash is present in only a fraction (approximately 10%) of patients with allergic tubulointerstitial nephritis, although at least one of these features is present in the majority of cases.^{1,4,5} The presence of eosinophils in urine can be helpful in suggesting the diagnosis and can be detected with the use of Wright, Giemsa, or Hansel staining⁶; however, the positive and negative predictive values of this finding are low.⁷ Eosinophiluria can occur with other conditions, including urinary tract infection, atheroembolic disease, and rapidly progressive glomerulonephritis, and can be absent in cases of acute tubulointerstitial nephritis, as it was in this case.

The initial approach to the treatment of allergic interstitial nephritis is to remove the offending agent. Conclusive data are lacking to support the use of immunosuppressants as adjunctive therapy. The findings in retrospective case series have been inconsistent. A study at a single tertiary referral center showed no significant difference in outcome between patients with acute tubulointerstitial nephritis who received glucocorticoids and those who did not.⁴ In contrast, a multi-center study showed that patients who received glucocorticoids had significantly lower serum creatinine levels than did those who were untreated; among the patients treated with glucocorticoids, those whose renal function completely recovered had started treatment earlier (13±10 days vs. 34±17 days after withdrawal of the culprit drug).⁵ Studies have been limited by the small number of cases in which acute tubulointerstitial nephritis is confirmed by means of biopsy, the variety of causes of these cases, and the variable duration of kidney injury before diagnosis.

Decisions regarding the use of glucocorticoid therapy in patients with acute tubulointerstitial nephritis must take into account the risks as well as the potential benefits. The use of glucocorticoids together with aspirin has been associated with an increased risk of upper gastrointestinal bleeding and perforation.⁸ The situation in this case was complicated by the fact that the presumed cause of the acute tubulointerstitial nephritis was a proton-pump

inhibitor. H₂-receptor blockers have also been implicated, although this complication appears to be rare.⁹

Although the patient first presented for urgent evaluation because of acute kidney injury, the sequence of events that led to the injury appears to have begun with his alcohol consumption and aspirin use (both taken for their cardioprotective effects), which probably contributed to his gastrointestinal symptoms. In turn, the treatment for his gastrointestinal symptoms (i.e., omeprazole) resulted in kidney injury. The treatment for the kidney injury — discontinuation of the proton-pump inhibitor and initiation of glucocorticoid therapy — put this patient at increased risk for upper gastrointestinal bleeding. Overall, this chain of events underscores the aphorism that medications can at times be thought of as poisons with beneficial side effects. In this case, as in many others, the treatment for one disease is the cause of another.

References

1. Baker RJ, Pusey CD. The changing profile of acute tubulointerstitial nephritis. *Nephrol Dial Transplant*. 2004; 19:8–11. [PubMed: 14671029]
2. Michel DM, Kelly CJ. Acute interstitial nephritis. *J Am Soc Nephrol*. 1998; 9:506–15. [PubMed: 9513915]
3. Brewster UC, Perazella MA. Proton pump inhibitors and the kidney: critical review. *Clin Nephrol*. 2007; 68:65–72. [PubMed: 17722704]
4. Clarkson MR, Giblin L, O'Connell FP, et al. Acute interstitial nephritis: clinical features and response to corticosteroid therapy. *Nephrol Dial Transplant*. 2004; 19:2778–83. [PubMed: 15340098]
5. González E, Gutiérrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int*. 2008; 73:940–6. [PubMed: 18185501]
6. Nolan CR III, Anger MS, Kelleher SP. Eosinophiluria — a new method of detection and definition of the clinical spectrum. *N Engl J Med*. 1986; 315:1516–9. [PubMed: 2431314]
7. Fletcher A. Eosinophiluria and acute interstitial nephritis. *N Engl J Med*. 2008; 358:1760–1. [PubMed: 18420515]
8. Nielsen GL, Sørensen HT, Mellemkjoer L, et al. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med*. 2001; 111:541–5. [PubMed: 11705430]
9. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H₂ receptor antagonists. *Drug Saf*. 2001; 24:39–57. [PubMed: 11219486]

Figure 1. Biopsy Specimen

Periodic acid–Schiff staining of a kidney-biopsy specimen reveals diffuse interstitial edema and inflammation (Panel A); at higher magnification (Panel B), a sample stained with hematoxylin and eosin shows invasion of the tubular structures and interstitium by a mixed inflammatory infiltrate with many lymphocytes and eosinophils. An electron micrograph (Panel C) reveals thin glomerular basement membranes (arrow). Images courtesy of Dr. Helmut Rennke.