

# A 78-Year-Old Woman with Proton Pump Inhibitor–Induced Acute Interstitial Nephritis

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**D**rug-induced acute interstitial nephritis (AIN) has been recognized and reported in the literature since the early 1960s.<sup>1–3</sup> Methicillin (now removed from the US market) was the first drug associated with AIN. With over 100 cases of methicillin-induced AIN reported, a definable clinical spectrum was observed, with renal failure occurring in approximately 50% of adults and 15% of children.<sup>4</sup> Classic extrarenal manifestations such as fever, rash, and eosinophilia were commonly seen and are suggestive of the diagnosis of drug-induced AIN, especially in cases involving  $\beta$ -lactam antibiotic drugs.<sup>4</sup> Since AIN was initially recognized, clinicians have identified other drugs that cause AIN; these cases often present without the classic extrarenal signs and symptoms described in methicillin-induced AIN.<sup>4</sup> A major drug class now associated with AIN is the proton pump inhibitor (PPI) drugs used to treat gastroesophageal reflux disease (GERD). This article reports the case of a 78-year-old woman with PPI-induced AIN who had been prescribed esomeprazole for suspected GERD. A review of the literature and discussion of the clinical features, diagnosis, and treatment of PPI-induced AIN are also provided.

## CASE PRESENTATION

### Initial Presentation and History

A 78-year-old woman was admitted for evaluation of rising serum creatinine concentration (SCr). Prior to admission, the patient underwent computed tomography with radiocontrast for periodic assessment of a thoracic aneurysm that had been found during abdominal aortic aneurysm repair 4 years ago. At the time that the CT was performed, the baseline SCr was 0.8 mg/dL (normal, 0.6–1.2 mg/dL). At a scheduled visit with her primary care physician 6 weeks later, the SCr was 2.6 mg/dL. Over the following 2 weeks, the SCr increased to 3.5 mg/dL, thus prompting hospital admis-

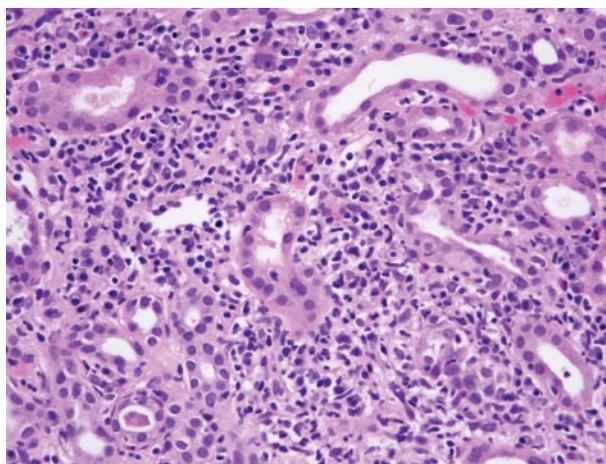
sion. Her only complaint to the primary care physician had been generalized malaise. At admission, the patient denied a history of recent prodromal illness, throat or sinus infection, rash, arthralgias, fevers, or chills. Urinalysis as an outpatient had shown pyuria with negative cultures. The patient had been treated with a short course of ciprofloxacin for sterile pyuria but was no longer taking this medication. At the current presentation, she denied dysuria, costovertebral tenderness, urgency, or frequency. Recent medication changes included discontinuation of ursodiol and enalapril (due to acute kidney injury) as well as the addition of hydralazine (for hypertension) and esomeprazole (for questionable GERD) within the last 2 months. Her past medical history was significant for a urethral dilation that occurred 10 years ago, longstanding overflow incontinence, a recent diagnosis of primary biliary cirrhosis, abdominal aortic aneurysm repair 4 years ago, a thoracic aneurysm diagnosed 4 years ago, longstanding hypertension, and longstanding chronic obstructive pulmonary disease.

### Physical Examination and Diagnostic Evaluation

On physical examination, the patient was in no acute distress. She had a blood pressure of 140/75 mm Hg, heart rate of 85 bpm, respiratory rate of 22 breaths/min, and temperature of 98.9°F. There was no evidence of edema or a skin rash. Urinalysis revealed 1+ protein, 1+ leukocyte esterase, 11 to 20 white blood cells per high power field, no red blood cells, and few bacteria. Urine culture was negative. Erythrocyte sedimentation rate

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**Figure.** Renal biopsy specimen from the case patient showing mixed inflammatory cell infiltrate into the interstitium consisting predominantly of plasma cells admixed with lymphocytes as well as some neutrophils and eosinophils. Mild tubulitis was also present (hemolysin and eosin, 400 $\times$ ).

obtained 2 weeks prior to admission was 104 mm/hr (normal, 0–20 mm/hr). White blood cell count was 12,400 cells/ $\mu$ L, with 62% polymorphonuclear neutrophils (normal, 56%), 28% lymphocytes (normal, 34%), and 2% eosinophils (normal, 2.7%). C3 complement was 120 mg/dL (normal, 90–180 mg/dL) and C4 complement was 33 mg/dL (normal, 10–40 mg/dL). Antinuclear antibody titer was 1:40 (normal, 1:20) with a speckled pattern. The urine protein to creatinine ratio was 1.0. Urine eosinophil count (Cytospin slide with Giemsa stain) was less than 1% (normal, < 1%). Kidney ultrasound showed an 11.4-cm left kidney and 12-cm right kidney without hydronephrosis or cortical echogenicity.

#### Clinical Course

Renal biopsy showed a mixed inflammatory cell infiltrate in the interstitium (consisting predominantly of plasma cells admixed with lymphocytes and some neutrophils and eosinophils) with normal glomerular pathology, which is consistent with acute AIN. Mild tubulitis was also present (**Figure**). As esomeprazole was the most likely cause of the patient's symptoms, it was stopped and prednisone (60 mg/day) was added. After 1 week of therapy, the patient's SCr decreased to 2.5 mg/dL. The patient was discharged on hospital day 8. After 2 weeks of treatment with prednisone followed by a steroid taper over a 3-week period, the SCr stabilized at 1.1 mg/dL with 1+ proteinuria on urinalysis at follow-up 4 weeks after hospital discharge.

#### DISCUSSION

Acute kidney injury has numerous causes, and thorough history taking, physical examination, and pertinent laboratory evaluation are needed to elucidate the underlying etiology. This patient had normal renal function at baseline. Neither the history nor the physical examination (eg, patient was not orthostatic) suggested a prerenal etiology for acute kidney injury. Likewise, a postrenal etiology (eg, obstruction) was ruled out by ultrasound. Urine studies, however, demonstrated pyuria and proteinuria, which pointed to a renal etiology; therefore we focused on the most common intrarenal causes given her presentation. Contrast-induced nephropathy was considered; however, this usually resolves over a period of a few days. In addition, the patient was at low risk for developing contrast-induced nephropathy given that she had normal renal function at baseline and did not have diabetes.<sup>5</sup> AIN was high on the list of differential diagnoses due to the patient's relatively nonspecific symptoms, her medication history, and urinalysis showing proteinuria, microscopic hematuria, and sterile pyuria. Renal biopsy ultimately confirmed this suspicion and did not show acute tubular necrosis, which would be seen in contrast-induced nephropathy.<sup>5</sup>

#### PPI-INDUCED ACUTE INTERSTITIAL NEPHRITIS

In the United States, GERD has surpassed abdominal pain as the most common gastroenterology-related diagnosis given in office visits, with over 5.5 million outpatient visits for GERD in 2002.<sup>6</sup> With the increased recognition and diagnosis of GERD, there has been a substantial increase in the use of PPIs. According to data from a commercial drug utilization audit that measures pharmaceutical products sold from retail pharmacies to consumers,<sup>7</sup> esomeprazole was the second most frequently prescribed drug and lansoprazole was the fifth most frequently prescribed in 2006, with prescriptions totaling \$5.1 billion and \$3.5 billion, respectively. As omeprazole has been available over the counter since 2003, the true number of patients taking this drug may be grossly underestimated.

In 1992, omeprazole was the first PPI reported to cause AIN.<sup>8</sup> Since then, many subsequent cases of drug-induced AIN associated with all 5 PPIs (omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole) have been reported.<sup>9</sup> The association of AIN with all 5 PPIs suggests that AIN is a class effect of PPIs, although no controlled studies have been conducted to evaluate this relationship (most reports are single cases or small studies).<sup>4,9,10</sup> Moreover, because clinicians may not be

aware of the association between PPIs and AIN, it is likely that many cases of acute kidney injury go undiagnosed.

In order to describe the clinical prodrome, prognosis, steroid responsiveness, and disease burden of PPI-induced AIN, we conducted a computerized search of the English language literature for articles that addressed PPI-induced AIN during the period of 1960 through June 2007 using MEDLINE, PREMEDLINE, and CINAHL. We used combinations of terms related to interstitial nephritis (AIN, acute interstitial nephritis, acute renal failure, acute kidney injury, acute tubulointerstitial nephritis) and proton pump inhibitors (PPI, rabeprazole, lansoprazole, omeprazole, pantoprazole, esomeprazole). We also examined the reference lists of all articles identified in the search as well as those of review articles. We identified 32 articles; however, 3 articles were excluded due to duplicate reports. The remaining 29 articles reviewed in detail included 94 biopsy-proven and 19 non-biopsy proven cases of PPI-induced AIN.<sup>8,10–37</sup> The results of this search are discussed in the following sections.

### Pathogenesis

Based on empiric evidence, the pathogenesis of PPI-induced AIN is likely to be triggered by a hypersensitivity immune reaction. Rossert<sup>4</sup> theorized that PPI-induced AIN is caused by antigen-induced immunity because AIN occurs in only some individuals, is not dose-dependent, is associated with extrarenal manifestations, and recurs after reexposure to drug. In our review of the literature, we found some cases where a PPI was reintroduced (either by trial or error) with rapid decline in kidney function, supporting the pathophysiology of a hypersensitivity immune reaction and confirming the diagnosis without biopsy.<sup>8,17,25</sup> Animal models suggest that PPIs or 1 of their metabolites might act as a hapten, which deposits in the renal interstitium as a circulating immune complex.<sup>32</sup> Both CD4 and CD8 T lymphocytes are seen in the inflammatory infiltrate, demonstrating a cell-mediated pathogenesis; however, the animal studies may offer a humoral explanation as well.<sup>36</sup> Further studies are specifically examining PPI benzimidazole derivatives and their metabolites to elucidate how they participate in molecular mimicry that triggers the immune response.<sup>32</sup>

### Clinical Features and Diagnosis

Fever, rash, and peripheral eosinophilia are commonly described in classic drug-induced AIN, with 79% of patients presenting with at least 1 sign or symptom.<sup>23</sup> As the present case and other reports of PPI-induced

AIN show, the clinical presentation of PPI-induced AIN is atypical, with only 5% to 6% of patients presenting with signs or symptoms of the clinical triad.<sup>26,32</sup> Because drug-induced AIN likely represents an idiosyncratic reaction, nonspecific signs and symptoms predominate. Most commonly, patients with PPI-induced AIN were older (median age, 74 yr), and they presented with symptoms of generalized fatigue, lethargy, nausea/vomiting, or fever.<sup>26,32</sup> In our review, the median age of patients was 67.4 years, and they were predominantly female (58%).<sup>8,10–37</sup> Patients were asymptomatic in 12% of reported cases.<sup>26,32</sup>

A thorough review of the patient's history including medication history as well as physical examination helps identify patients at risk for drug-induced AIN; however, renal biopsy or withdrawal of the offending drug confirms the diagnosis. The most common laboratory findings of PPI-induced AIN were sterile pyuria, proteinuria, and hematuria, which support the diagnosis.<sup>36</sup> The presence of eosinophiluria helps support the diagnosis of typical drug-induced AIN if Hansel stain is used; however, this finding occurs in less than 20% of PPI-induced cases.<sup>36</sup> As seen with the case patient, patients may present with elevated creatinine and acute kidney injury; however, symptom onset varies among cohorts studied, ranging from 1 week to 9 months after introduction of the PPI.<sup>8,10–37</sup> Median SCr level at presentation in our review of the literature was 5.02 mg/dL.<sup>8,10–37</sup> Imaging studies do not generally establish the diagnosis of PPI-induced AIN, although the kidneys should appear normal. Renal ultrasound is critical for ruling out an obstructive or postrenal cause of acute kidney injury.

The gold standard for diagnosing AIN is renal biopsy, which typically shows a normal glomerulus with dense interstitial infiltrate consisting mainly of lymphocytes, plasma cells, and eosinophils,<sup>24</sup> as seen in this case patient. Besides the more common AIN, there have been rare cases with perinuclear antineutrophilic cytoplasmic antibody-positive vasculitis and histiocytic granulomatous interstitial nephritis associated with omeprazole.<sup>17,25</sup> With a biopsy that supports the diagnosis, all other medications must be ruled out as potential causes in order to confirm the diagnosis of PPI-induced AIN.

### Treatment

Treatment recommendations for PPI-induced AIN are based on empiric and observational studies, but no robust clinical trials have been conducted. The mainstay of therapy is supportive care with discontinuation of the PPI. Immunosuppressive agents are used if there is no substantial improvement in renal function after

withdrawing the agent, if kidney failure is severe, or if biopsy shows high activity (ie, intense cellular infiltrate) with little fibrosis. Corticosteroids are most commonly used due to the aforementioned manifestations of hypersensitivity as a pathogenetic mechanism.<sup>2,32,38,39</sup> At present, no studies have been conducted to determine whether drug cessation alone or with steroid treatment is superior in PPI-induced AIN. Small series and retrospective cohorts that primarily consisted of patients with methicillin-induced AIN showed better renal recovery in treated patients than in controls.<sup>2–4,38</sup> One series demonstrated that 8 of 14 patients diagnosed with methicillin-induced AIN who received oral prednisone 60 mg/day recovered in 9 days versus 54 days in those not treated with steroids.<sup>38</sup> In another series of 27 patients with biopsy-proven AIN, 10 patients whose renal function further deteriorated despite removing the offending drug were treated with stress dose methylprednisolone or oral prednisone. Six patients had normal SCr levels within 1 month of treatment, and the remaining 4 had partial improvement of kidney function.<sup>2</sup> In our review of the literature, improvement was demonstrated in cases treated with cessation of the drug and/or steroids; however, the mean decrease in SCr was no different in the patients treated only with PPI cessation as compared with patients treated with PPI removal and corticosteroids (3.26 mg/dL versus 3.29 mg/dL), respectively.<sup>8,10–37</sup> Despite the lack of compelling evidence, many clinicians suggest treatment of drug-induced AIN with prednisone 1 mg/kg/day for 1 to 2 months, especially if the biopsy reveals dense acute interstitial inflammation.<sup>10,32</sup> If the biopsy shows a significant degree of interstitial fibrosis, corticosteroids are not likely to be beneficial.<sup>10,32</sup> Recently, mycophenolate mofetil has also been shown to be effective in steroid-recalcitrant cases.<sup>39</sup>

### Prognosis

Despite recovery in most cases of PPI-induced interstitial nephritis, many patients are left with some renal impairment classified as chronic kidney disease (CKD).<sup>10,36</sup> In the case patient as well as the review of included studies, we found that many patients had a persistent elevation of SCr after recovery from renal injury. Overall, the median posttreatment SCr level was 2.76 mg/dL, with a median SCr of 1.6 mg/dL for patients who received steroids in addition to PPI withdrawal and a median of 2.1 mg/dL for patients who only underwent PPI withdrawal.<sup>8,10–37</sup> In 1 larger cohort study,<sup>37</sup> 12 out of 14 patients with PPI-induced AIN had persistent SCr elevations and CKD. The literature documents persistent SCr elevation in up to 40% of patients with AIN caused by a drug

other than methicillin.<sup>4</sup> Therefore, renal injury from PPI-induced AIN does confer lasting damage in many patients and, on rare occasions, dialysis dependence.<sup>12,26,37</sup>

### Disease Burden

PPIs appear to be the most common cause of AIN based on multiple large hospital-based case series.<sup>31,36</sup> For example, 35 (32%) of 110 cases of drug-induced AIN reported to the Centre for Adverse Reactions Monitoring (CARM) in New Zealand were attributed to PPIs.<sup>10,37</sup> In a review of 296 consecutive renal biopsies that occurred during a 4.5-year period in a UK hospital, biopsy-proven AIN was identified in 24 (8.1%) cases. Eight of 14 cases of suspected drug-induced AIN were positively attributed to the PPIs omeprazole and lansoprazole.<sup>34</sup> This evidence challenges the concept that nonsteroidal anti-inflammatory drugs,  $\beta$ -lactam antibiotic drugs, and diuretic agents are the most common causes of drug-induced AIN.

### CONCLUSION

With the growing usage of PPIs due to increased diagnosis of GERD and other acid-related gastrointestinal disorders, the potential for an increase in the number of cases of acute kidney injury and subsequent CKD is high. Therefore, primary care physicians and nephrologists must be aware that PPIs are an increasingly frequent cause of AIN and work together to rapidly identify and treat this disorder when it occurs. Patients who develop CKD despite removing the offending agent require follow-up by nephrologists to assist in managing complications associated with CKD. **HP**

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