CLINICAL VIGNETTE

Fever of Unknown Origin, a Rare Presenting Feature of Acute Interstitial Nephritis from a Commonly Prescribed Medication

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Case Presentation

A 68-year-old female who had been relatively healthy throughout her life except for a history of hypothyroidism and gastroesophageal reflux disease was referred to Nephrology for evaluation of acute kidney injury. The patient had symptoms of urinary tract infection including fever and chills for three days and was prescribed ciprofloxacin for one week. After completing the course of ciprofloxacin patient's urinary symptoms resolved however she continued to have fever as high as 102 F and chills. She had an associated non-productive cough. She did not have any night sweats, weight loss, dysuria, urinary frequency, headache, neck stiffness, diarrhea or skin rash. She had no recent travel or animal exposures. She was up to date on her Health Maintenance with a prior hysterectomy.

Medications included Omeprazole 20 mg daily (started 2 months prior), Famotidine 40 mg daily, Levothyroxine 50 mcg daily and estradiol 0.05 mg patch. She occasionally used OTC naproxine, once a week as needed.

On exam, temperature was 98.1 F, Blood pressure 128/66 mmHg, HR 65, O2 saturation 98%. She was a well appearing woman with no significant abnormal findings on exam.

Her initial evaluation with her primary care physician revealed elevated serum creatinine at 1.4 from prior baseline of 1.1. She also had elevated sedimentation rate of 67 and CRP 74.6. Hemoglobin was 10.8, with normal eosinophils and ferritin, negative hepatitis panel, ANA was positive at 1:40 speckled with negative dsDNA. Coccidiodomycosis serology and other infectious serologies were also negative. CT of the abdomen pelvis was notable for a 3.7 mm non-obstructing kidney stone. Echocardiogram was unremarkable.

The patient continued to have fever and chills primarily at night, as high as 101.5 F. Repeat labs continued to show elevated ESR and CRP, and serum creatinine as high as 1.7 with no improvement. She had a kidney biopsy performed which revealed marked tubulointerstitial inflammation with rare eosinophils consistent with antibiotic induced acute interstitial nephritis. There was also moderate chronic tubulointerstitial changes.

About eight weeks after the kidney biopsy patient's serum creatinine improved to 1.2 and her ESR improved as well. Since then her creatinine has remained at around 0.9 to 1.1 for about a year. Fever and chills resolved around the same time as well. Her proton pump inhibitor was discontinued about 6 weeks before her biopsy and she completed her week of ciprofloxacin 8 weeks before her biopsy.

Discussion

Our patient with persistent fever and chills, acute kidney injury from biopsy proven acute interstitial nephritis (AIN) after a 7-day course of ciprofloxacin had symptoms for more than 3 months before resolution. She was also on a proton pump inhibitor (PPI) which was also stopped 2 months prior to resolution.

AIN is an underdiagnosed cause of acute kidney injury (AKI). It is estimated to account for 15-20 percent of the cases of AKI. The central component in AIN is altered tubular function, which usually precedes the decrease in filtration rate and is characterized by an inflammatory infiltrate in the kidney interstitium. Drugs account for 70% of all cases. Other autoimmune disorders such as systemic lupus erythematosus, sarcoidosis and Sjogrens syndrome can cause AIN as well. Any drug can cause AIN and the most common drugs causing AIN include NSAIDs including COX-2 inhibitors, penicillins and cephalosporins, Rifampin, and Ciprofloxacin. Other fluoroquinolones, sulfonamides including trimethoprim-sulfamethoxazole, allopurinol, Proton pump inhibitors (PPIs) such as Omeprazole have also been linked to AIN.

Patients may present with nonspecific signs and symptoms such as nausea, vomiting, malaise; however many patients are asymptomatic. Patients with drug induced AIN commonly report fever, rash and eosinophilia. However, in a recent review of three series that totaled 128 patients, reported lower prevalence of these findings. Rash was seen in 15 percent, fever in 27 percent, eosinophilia in 23 percent and the triad of all these symptoms in only 10 percent of the patients.[1,2] The onset of drug-induced AIN following drug exposure may range from 3-5 days, to as long as several weeks to many months.

Several studies reported an association between PPIs and AIN. It is often difficult to establish a temporal relationship between PPI use and AIN as the symptoms associated with PPI induced

AIN are not severe. The detection of AIN after starting a PPI is usually 10-11 weeks after starting the drug.[3,4] As PPIs are one of the most frequently prescribed drugs, studies suggested that repeated episodes of PPI-induced AIN, many of them un-detected, can contribute to the development of chronic kidney disease (CKD). Epidemiological studies have shown an association between consumption of PPI and the presence of CKD.[5,6]

The development of drug-induced AIN is not dose dependent, and recurrence or exacerbation can occur with a second exposure to the same or a related drug. Once a diagnosis is made by kidney biopsy, the underlying cause should be determined. Discontinuation of the potential causative agent is mainstay of therapy. Immunosuppressive therapy with glucocorticoids have been used to treat AIN that persists despite discontinuation of offending agent. The benefits of therapy are inconclusive due to lack of randomized, controlled trials.

Conclusion

In conclusion, our 68-year-old female patient who presented with unexplained and acute kidney injury had AIN most likely related to ciprofloxacin, possibly complicated by PPI use. Most cases of AIN due to drugs improve spontaneously. Kidney function however may not return to baseline. Our patient's kidney function improved to baseline several months after the initial insult. It is important to discontinue potential offending drugs and consider a kidney biopsy if kidney function does not improve.

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