CLINICAL VIGNETTE

Two Unusual Inpatient Presentations of Acute Allergic Interstitial Nephritis (AIN)
AIN: Using Non-Invasive Diagnosis When Biopsy Risk is High

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Introduction

Acute kidney injury (AKI) occurs in 5-7% of hospitalized patients in the United States and acute tubular necrosis (ATN) and acute allergic interstitial nephritis (AIN) represent two common causes.[1] Studies of AKI estimate that nearly 15-20% of cases of patients hospitalized with acute kidney injury are due to AIN.[2] Drug induced disease is thought to be responsible for 60-70% of these cases.[3] Urinary biomarkers like urine eosinophilia are not as specific as previously thought, and the clinical triad of rash, renal failure, and fever is only seen in a minority of cases.[3] The most important clinical clue is often the timing of the renal failure as relates to the initiation of a suspect drug that is known to cause interstitial nephritis.[3]

Early recognition is of paramount importance and allows discontinuation of the offending agent as the first step of care. Corticosteroids have correlated with improvement in renal function for some patients, but they are not proven to work in every case. Additionally, the side effects of steroids can be severe in patients with high blood urea, diabetics, and in patients who are prone to infections.[4]

The standard method of diagnosis besides clinical deduction is by renal biopsy, which is sensitive and specific for the disease but invasive.[3,4] Gallium scintigraphy may offer a clue in the right clinical context, but is not as reliable as biopsy.[5] The sensitivity and specificity of gallium scanning for AIN is reported as 61% and 75% respectively in one series,[5] though historically sensitivity values varied between 58-100%.[5]

We report two patients with atypical presentations of AIN on anticoagulation making renal biopsy potentially risky. One patient was diagnosed based on clinical suspicion and in the second reported case with gallium scintigraphy. One patient was treated successfully with withdrawal of the offending agent (naficillin) and one was treated with drug withdrawal (meropenem and phenazopyridine) and high dose corticosteroids. In the second case the patient was able to come off of hemodialytic support and regained her renal function. In both cases the clinical timing and a high suspicion were most helpful to making the diagnosis. Supporting lab tests including urinary eosinophils, urinalysis, and peripheral eosinophils were not as clear. The clinical course was more similar to ATN than AIN in the second case and nuclear medicine testing playing an adjunct role.

Case Report 1

The first case involves a previously active 92 year-old male with well controlled atrial fibrillation on warfarin, hypertension, and coronary artery disease. He had undergone excision of a small right scalp keratosis a few days prior to presentation and subsequently developed worsening fatigue and generalized weakness to where he was unable to ambulate or raise himself out of bed leading to a fall at home. On hospital day 1, he was bacteremic with *Staphylococcus aureus* and started on empiric vancomycin and nafcillin. On hospital day two, E. coli bacteremia was also diagnosed. The source of these 2 infections was suspected skin injury from fall or the recent excision scalp or urinary tract infection. Additionally on the second hospital day he developed AKI with a precipitous rise in his serum creatinine from an initial value of 0.97 mg/dl to 1.71 mg/dL. The antibiotic was initially changed to cefazolin, but on hospital day three there was a further rise in his creatinine level to 2.94 mg/dL. His antibiotics were again changed to meropenem and daptomycin.

With these changes, his creatinine slowly improved, and on hospital day six he was switched to nafcillin for MSSA (with plan for six week course given high risk of TEE which wasn't pursued) and ceftriaxone for *E. coli* (with plan for two week course). His urine eosinophils were negative, complete blood count showed only a borderline level of peripheral eosinophilia, and renal biopsy was relatively contraindicated given anticoagulant use. Nephrology raised concerns about AIN, but infectious disease insisted that the presentation was atypical for AIN, and that the staphylococcal bacteremia was a high-risk infection for life threatening endocarditis. He was discharged to home on hos-pital day nine with nafcillin and with creatinine value of 2.01 mg/dL.

Unfortunately, our patient was readmitted to the hospital six days after discharge for dehydration due to diarrhea. His serum creatinine was elevated again to 2.24 mg/dL which improved with fluids and was discharged again to home on day eleven with creatinine 1.75 mg/dL on a lower dose of nafcillin (1 gm q6 hrs rather than 2 gm q4 hrs). He returned to the hospital again on day seventeen with generalized weakness, confusion, and AKI with creatinine 2.27 mg/dL. Due to pyuria from recurrent *E. coli* UTI, he was again placed on ceftriaxone, then aztreonam without resolution of his acute kidney injury.

His creatinine peaked at 3.0 mg/dL forty-two days after his initial admission and then slowly improved to 1.9 mg/dL prior to discharge to rehab facility on day forty nine. Renal biopsy was judged to be too risky by the treating team and family in setting of anticoagulation. During this last period peripheral eosinophils on CBC rose to a peak of 8.9% on day thirty-five, and urine eosinophils eventualy returned positive. The timing of AKI with nafcillin initiation, the more typical pyuria and urine eosinophiluria during the final hospitalization, and the improvement of renal function with holding nafcillin all provide support for the diagnosis of AIN. Further, the patient also developed drug induced hepatitis with aspartate aminotransferase and alanine aminotransferase in the 1000's that responded with holding nafcillin. The clinical picture thus suggested drug induced hepatitis as well as drug induced AIN. Figure 1A graphs urine and peripheral eosinophilia, pyuria, hematuria, and AKI. Figure 1B reviews the trend of the liver enzymes elevation noted during last hospitalization.

Figure 1

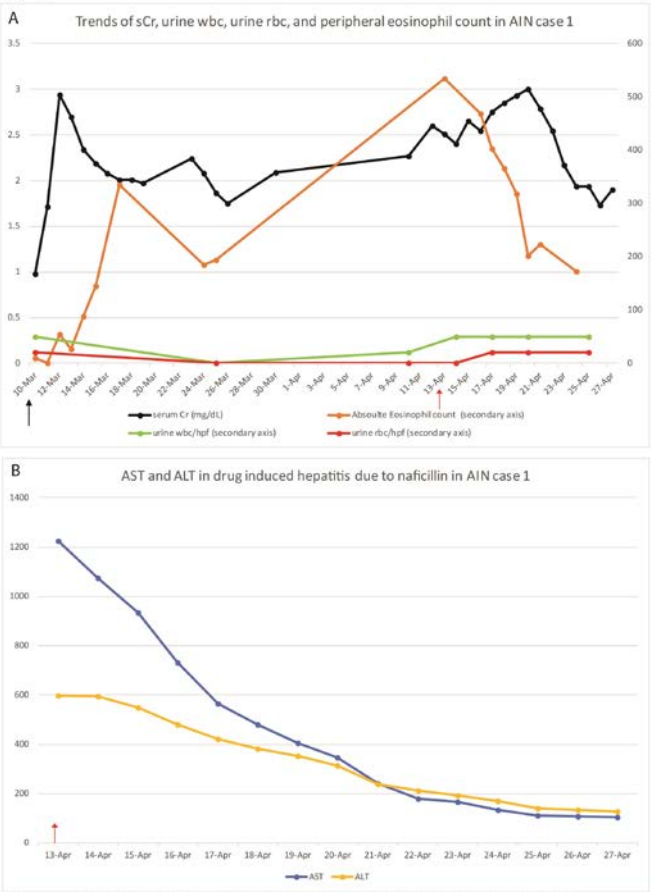

Figure 1 **–** A) Trends of sCr, urine wbc, urine rbc, and peripheral eosinophil count in AIN case 1 AIN=acute interstitial nephritis, Cr=Creatinine, hpf=high power field, sCr= serum creatinine, rbc=red blood cell, wbc=white blood cell. Black arrow start of nafcillin, red arrow stop of nafcillin. B) AST and ALT in drug induced hepatitis due to naficillin in AIN case 1 AST=aspartate aminotreansferase, ALT= Alanine aminotransferase. Stop of naficillin.

Case Report 2

A 40-year-old female, was admitted after cardiac arrest. She was 10 days post anterior ST elevation myocardial infarction (STEMI) with drug eluting stent (DES) placed to ostial left anterior descending (LAD) artery with ischemic cardiomyopathy with echocardiogram showing left ventricular ejection fraction (LVEF) of 20-25%. Her past medical history was remarkable for morbid obesity, recently diagnosed poorly controlled diabetes mellitus with A1C of 14%. She was at her primary care office for follow up when she suffered a cardiac arrest. Advanced cardiac life support protocol achieved return of spontaneous circulation (ROSC). She was transported to the emergency department at a nearby community hospital where she suffered another cardiac arrest followed by ROSC.

She was emergently taken to cardiac catheterization lab. Coronary angiography revealed subacute in stent thrombosis and a second stent was placed along with a temporary ventricular assist device (Impella). She was transferred to ICU on mechanical ventilation in cardiogenic shock, requiring inotropic and vasopressor support. She developed acute kidney injury (AKI) due to acute tubular necrosis (ATN) due to cardiogenic shock and a component of contrast induced nephropathy (CIN) with peak creatinine (Cr) of 1.68 mg/dL (Cr on admission of 1.54 mg/dL). Subsequent AKI was due to cardiorenal syndrome with peak creatinine of 2.04 mg/dL (day nineteen).

In an effort to improve urine output, she was started on a trial of inotropic support (dopamine), albumin infusion, and continuous infusion of loop diuretic. Due to oliguria, refractory pulmonary edema, volume overload, and inability to wean from ventilator, she required intermittent hemodialysis for 5 days, facilitating extubation. On hospital day sixteen, she was started on meropenem for ventilator associated pneumonia. Bronchoscopic aspirate grew *Klebsiella pneumonia* and antibiotics were changed to ceftriaxone and tobramycin for completion of seven day course. Additionally, she was found to have right lower extremity deep vein thrombosis on day seventeen and was started on apixaban.

On hospital day 24 she was transferred to ICU and continued to be managed medically for severe ischemic cardiomyopathy, insulin dependent diabetes, urinary retention requiring intermittent catheterizations, advancement of diet, and physical therapy. On day thirty, she had placement of automated implantable cardioverter defribillator (AICD). On hospital day forty-one, she was started on meropenem for *Enterobacter cloaca* UTI. Creatinine was 1.32 mg/dL and one week later had increased to 5.13 mg/dL.

Urine electrolytes suggested prerenal etiology (urine sodium 16mmol/L; FeNa 0.2%), but patient was clinically volume overloaded. Urine output and creatinine did not improve with IV albumin and IV furosemide making cardiorenal syndrome unlikely. She had no contrast exposure within the time frame of this AKI and had no clear risk factors for ATN such as sepsis or sustained hypotension. Renal thromboembolic disease was considered, but was unlikely, and difficult to diag-

nose. Renal sonogram showed no significant abnormality and doppler ultrasound of the bilateral renal arteries, revealed normal flow pattern. Suspicion for thrombotic microangiopathy (TMA) was low given normal platelet count (low 200s), elevated haptoglobin (255mg/dL), minimally elevated LDH (340 units/L), complement levels were within normal limits and ADAMTS13 activity assay did not show deficiency (67%). Rare urine eosinophils were seen on smear on day forty-four and day forty-seven and serum eosinophils were 1.3% on day forty-four. Due to the bleeding risk while on antiplatelet (prasugrel) therapy and anticoagulation (apixiban), renal biopsy was felt to be relatively contra indicated.

On day forty-six meropenem was held due to concern for AIN. The next day she started iHD on which was repeated the following day. Creatinine began trending down, urine output increased, and she did not require additional dialysis. On hospital day fifty-one, NM Gallium scan showed activity in both kidneys, suggestive of acute interstitial nephritis (AIN). She was started on prednisone 60 mg daily and the dose was slowly tapered. Her renal function improved significantly, with creatinine trending down to 1.30 mg/dL upon discharge (peak was 5.13 mg/dL on day forty-seven). On hospital day sixty, she was discharged to acute rehab for management of physical deconditioning.

Figure 2

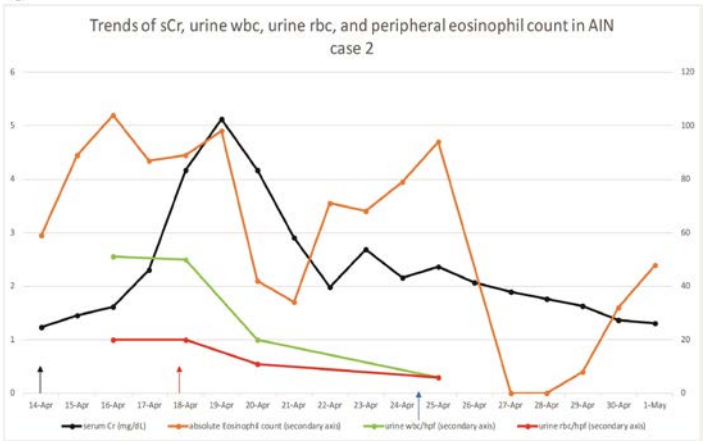

Figure 2 - Trends of sCr, urine wbc, urine rbc for AIN case 2 AIN = acute interstitial nephritis, Cr = Creatinine, hpf = high power field, sCr = serum creatinine, rbc = red blood cell, wbc = white blood cell. Black arrow start of meropenem, blue arrow start of high dose steroids, red arrow stop of meropenem.

Figure 3

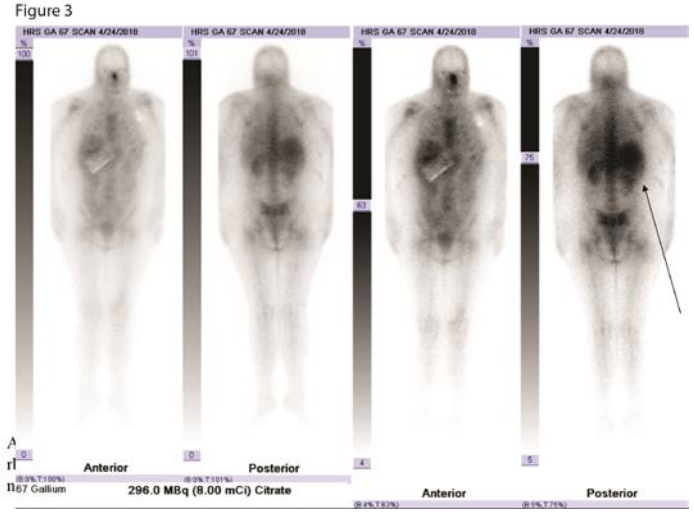

Figure 3 - Gallium scan for AIN case 2.

Discussion

Two cases are presented that showed varying presentation of AIN. In the first case, the only strong clue to AIN was the timing of AKI relative to nafcillin start. The urine and peripheral blood count were not typical for AIN. The third hospitalization was more consistent with the expected phenotype, and the finding of a drug induced hepatitis helped suggest a systemic allergic reaction affecting the kidney and liver.

In the second case the severe oliguria seen is not typical of AIN. The only exposure that seemed to suggest AIN was that after ruling out all other nephrotoxins, the possibility of AIN due to meropenem was a possible hypothesis. The gallium scan was ultimately the most helpful in this case since the urine and eosinophilic parameters were atypical. It is concluded that the timing of AKI is a very powerful clue to etiology. These cases also show the difficulty in utilizing clinical clues alone to diagnose AIN when renal biopsy is contraindicated or comes with a high risk.

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