AKI in a Hospitalized Patient with Cellulitis

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Summary

AKI occurs commonly in hospitalized patients with multiple comorbidities. In this Attending Rounds, a woman with AKI in the setting of an infection, use of antibiotics and other medications, bacteremia, and hypotension is considered. Such patients lead to a broad differential diagnosis for AKI including prerenal AKI, acute tubular injury/acute tubular necrosis, infection-related GN, and drug-induced acute interstitial nephritis. The roles of an accurate history, physical examination, laboratory data, and kidney biopsy are highlighted in establishing the correct diagnosis in such patients.

Clin J Am Soc Nephrol 8: 658–664, 2013. doi: 10.2215/CJN.09370912

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Introduction

A 68-year-old woman was admitted to the hospital with fever, shaking chills, and 3 days of worsening left lower extremity pain with swelling and erythema consistent with acute cellulitis. One week before admission, she tripped while walking at home and injured her left leg against the edge of the coffee table. Over the next few days, the leg became progressively more painful with swelling and erythema.

Past medical history was pertinent with stage 3 CKD (baseline serum creatinine 1.3 mg/dl), chronic obstructive pulmonary disease, longstanding hypertension, moderate aortic stenosis (AS), coronary artery disease, ischemic cardiomyopathy (ejection fraction, 30%), osteoporosis, and anemia. Medications on admission included losartan, chlorthalidone, carvedilol, cholecalciferol, budesonide/formoterol, montelukast, aspirin, clopidogrel, and iron sulfate.

On admission, her vital signs were as follows: BP 112/65 mmHg, pulse 108/min, respirations 22/min, weight 58 kg, temperature 101.8°F, and O_2 saturation 94%. Examination revealed decreased breath sounds with minimal basilar crackles, 2/6 systolic murmur radiating to the carotids, benign abdomen with positive bruit, 2+ pitting edema with erythema with some crusting and blistering of her left foot and calf, and trace edema of the right ankle. Skin had no rash or petechiae.

Admission laboratory values are noted in Table 1. Urinalysis revealed specific gravity (SG) 1.019, pH 5.5, and trace protein; the results were negative for blood, glucose, and leukocyte esterase. She was given intravenous piperacillin/tazobactam (3.375 every 6 hours) and normal saline at 125 ml/h. On day 4 of hospitalization, she developed hypotension (75–96/40–54 mmHg), tachycardia (98–114/min), and hypoxemia (83% O_2 saturation) requiring 2 L of nasal cannula oxygen therapy and transfer to the medical intensive care unit (MICU). Losartan was held and intravenous fluids were discontinued.

Blood cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA) and 750 mg of intravenous vancomycin twice daily was added. Low-dose intravenous NE was initiated for ongoing hypotension (80s/50s mmHg) with improvement to systolic BP >100 mmHg. One unit of packed red blood cells (RBCs) was administered along with 40 mg of intravenous furosemide. On day 6, she was disoriented, appeared dyspneic, and required increased nasal oxygen (4 L) to maintain O_2 saturation >90%. Examination revealed bilateral crackles over the lower one-quarter of the lung fields, and chest roentgenogram revealed mild pulmonary edema with small bilateral effusions. A bladder catheter was placed; 60 mg of intravenous furosemide was given and a nephrology consultation obtained on day 7 for rising serum creatinine (Table 1).

When seen by the nephrology consultant, the patient's vital signs were as follows: BP 122/72 mmHg, pulse 98/min, temperature 99°F, O_2 saturation 92% on 4-L nasal cannula, and central venous pressure 16 cm H_2O. Urine output was 850 ml over the past 24 hours. Physical examination revealed prominent jugular venous pulsations, bilateral lung crackles, an AS murmur with S4 gallop, and pitting sacral and lower extremity edema. There was no skin rash, and left leg cellulitis appeared somewhat improved with less erythema than described previously. BUN and serum creatinine were 44 mg/dl and 2.85 mg/dl, respectively, whereas an increased anion gap (AG) metabolic acidosis was noted (albumin corrected AG 18). White blood cell (WBC) count was $13.7\times10^3/\mu$l with 2% eosinophils. Her urinalysis revealed SG 1.017, pH 6.0, 2+ protein, 1+ blood, and 1 + leukocyte esterase, and was otherwise negative. Urine for eosinophils by Wright stain was negative. Renal ultrasonography noted bilateral moderately echogenic kidneys of normal size without hydronephrosis, cysts, or nephrolithiasis.

The MICU team had obtained urine chemistries to calculate fractional excretion (FE) of sodium (Na) (2.1%) and FEurea (45%), because the patient had received intravenous furosemide 5 hours before the

Table 1. Patient laboratory values

Laboratory Values	Day 0	Day 1	Day 3	Day 5	Day 6	Day 7	Day 8	Day 14	Day 22
Clinical events	Hospital admission; P/T		Vancomycin (day 4)	MICU		Renal consult		Steroid therapy	Hospital discharge
Intake/output (ml)	—	2810/1230	2015/1350	1855/1510	2105/850	1960/1015	1715/1125	1555/1875	—
Sodium (mEq/L)	136	135	132	130	133	131	127	131	137
Potassium (mEq/L)	3.9	3.7	3.8	4.7	4.6	5.1	5.5	5.3	3.9
Chloride (mEq/L)	98	100	99	97	99	98	95	97	98
Total CO_2 (mEq/L)	28	24	20	21	19	18	17	16	26
BUN (mg/dl)	31	25	23	26	32	44	52	81	45
Serum creatinine (mg/dl)	1.41	1.23	1.28	1.38	1.42	2.85	3.71	6.62	1.52
WBC ($\times 10^3/\mu l$)	22.4	20.7	23.5	19.6	16.4	13.7	12.2	8.8	14.5
Hemoglobin (g/dl)	9.1	8.2	7.5	8.7	8.4	8.1	8.0	7.5	8.7
Platelets ($\times 10^3$/L)	244	206	192	188	175	165	188	195	255

P/T, piperacillin/tazobactam; MICU, medical intensive care unit; WBC, white blood cell.

urine collection. The nephrologist performed microscopy of the spun urine sediment, which demonstrated 5–8 isomorphic RBCs per high-power field (HPF), 6–10 WBCs per HPF (Figure 1A), 1–3 renal tubular epithelial cells (RTECs) per HPF, 1–3 granular casts per low-power field (LPF), and 1–3 hyaline casts per LPF, but no cellular casts.

Case Discussion

Differential Diagnosis

The patient in this case developed hospital-acquired AKI in the setting of treatment for left leg cellulitis complicated by MRSA bacteremia. A couple of points are worth making in regard to the patient's comorbidities and risk for AKI. The baseline serum creatinine of 1.3 mg/dl seen in this patient is often unrecognized as being CKD by healthcare providers. Underlying CKD, in this case stage 3 with estimated GFR of 41 ml/min per 1.73 m^2, along with longstanding hypertension and congestive cardiomyopathy increases risk for AKI (1). Therapy for cellulitis and bacteremia may expose the patient to potentially nephrotoxic antimicrobial agents, and her underlying CKD will require dose adjustments to avoid incorrect antibiotic dosing. The

Figure 1. | Urine microscopy and kidney biopsy result. (A) Urine microscopy reveals many white blood cells and few isomorphic red blood cells. (B) Renal histopathology under light microscopy reveals diffuse cellular infiltrate consisting of lymphocytes, plasma cells, and eosinophils.

clinician must recognize these nuances in this and other similarly complex patients.

The cause of AKI in this patient is not obvious at first glance and numerous possibilities exist. Epidemiologically, the two most likely causes of AKI in the hospitalized patient are prerenal AKI and acute tubular injury/necrosis (ATI/ATN). Both are certainly real possibilities in this patient. Other possible causes of AKI include postinfectious GN (PIGN) and drug-induced acute interstitial nephritis (AIN). Each of these possibilities will be discussed reviewing their clinical features, weighing their likelihood as the cause of AKI, and discussing how the correct diagnosis is ultimately confirmed.

Prerenal or hemodynamic AKI may result from either true or effective volume depletion, especially in patients such as this who have underlying CKD and are receiving renin-angiotensin system blockers (2). True volume depletion is very unlikely as the patient was given >4 L of normal saline, had no evidence of excessive renal or extrarenal losses, and examination was remarkable for total body salt and water overload with peripheral and pulmonary edema. Effective volume depletion with prerenal AKI is possible because the patient had an underlying ischemic cardiomyopathy with AS and had clinical evidence suggestive of pulmonary vascular congestion. An echocardiogram was performed in the patient to assess cardiac function. No valvular vegetations and no changes in ejection fraction, degree of AS, or overall cardiac function were noted. Data not supportive of prerenal AKI are FENa and FEurea above prerenal AKI cutoffs, and an active urine sediment (RTECs and granular casts), both of which suggest renal tubular dysfunction and injury. However, the limitations of both FENa and FEurea must be considered. Underlying CKD as in this patient, as well as glucosuria, bicarbonaturia, salt-wasting disorders, and obtaining the test after intravenous fluid administration may be associated with elevated FENa/FEurea despite the presence of prerenal AKI. In addition, these two tests can be <1% and <35% (consistent with prerenal AKI), respectively, despite the presence of ATN/ATI in the setting of sepsis, hemoglobinuria/myoglobinuria, radiocontrast, nonoliguria, heart failure, and advanced cirrhosis.

Ischemic and nephrotoxic ATI/ATN are common causes of AKI. In this patient, ischemic tubular injury is possible based on several lines of evidence. In the setting of underlying CKD and hypertensive arteriosclerosis, compounded by therapy with an angiotensin-receptor blocker, the patient has impaired ability to tolerate reduced renal perfusion associated with hypotension (3). Sepsis with AKI is also possible, which can lead to ischemic tubular injury and other forms of kidney injury such as nonspecific acute tubulointerstitial lesions, vascular congestion with intrarenal hemorrhage, glomerular injury, and infectious pyelonephritis. As noted previously, the urine chemistry results favor reduced tubular reabsorptive capacity consistent with tubular injury. Finally, RTECs and granular casts on urine microscopy may be seen with ischemic or nephrotoxic ATI/ATN. Drug-induced kidney injury is unlikely in this patient, because she did not receive any directly nephrotoxic medications before developing AKI.

Acute PIGN from MRSA cellulitis and bacteremia should be strongly considered as a potential cause of AKI. MRSA infection is well described to promote an immune-complex GN in hospitalized adults (4). Although some forms of PIGN develop several weeks after infection, MRSA-induced PIGN can occur within several days of infection and cause severe AKI (4). Active urine sediment with dysmorphic RBCs, WBCs, and RBC casts is often seen along with proteinuria (commonly nephrotic range). Purpuric lesions and hypocomplementemia may also occur. Our patient did not have rash or purpura. Serum complement levels were measured and found to be normal, whereas spot urine protein/creatinine was 1.05. Repeat urine microscopy on day 8 revealed 5–10 isomorphic RBCs per HPF, 10–15 WBCs per HPF, 5–8 RTECs per HPF, 3–5 granular casts per LPF, and now 1–3 WBC casts per LPF, raising concern for AIN. Because both acute PIGN and AIN were possible, a kidney biopsy was performed. Findings diagnostic of drug-induced AIN (Figure 1B), in this case the likely culprit being piperacillin/tazobactam, were noted. The combination of culprit drug exposure, timing of AKI, and interstitial cellular infiltrate containing numerous eosinophils favored drug-induced AIN (DAIN) rather than infection-associated AIN, which is more commonly associated with polymorphonuclear cells or plasma cells.

DAIN

DAIN is an increasingly common cause of hospital-acquired AKI. It is a clinical-pathologic entity in which AKI is accompanied by histologic findings of inflammatory cells and edema within the interstitium, and tubulitis, sometimes with granuloma formation (5,6). DAIN is seen in approximately 3% of all renal biopsies (7–9), but this increases to as high as 27% when only patients with unexplained AKI are included (8–10). Pooled data from several studies describe medications (71.1% of 128 cases) as the most common cause of AIN (11). Similarly, 58% of 160 AIN cases from the UK Medical Research Council were due to DAIN (8).

Clinical Presentation. The clinical presentation of DAIN is quite variable; most patients come to attention when kidney injury is discovered on laboratory testing (12,13). As seen in our case, initial consideration of DAIN began when an unexplained rise in serum creatinine occurred after exposure to new medications. The clinical picture is often complicated by multiple processes ongoing during hospitalization such as systemic infection and bouts of hemodynamic instability. DAIN often manifests as a slow rise in serum creatinine with preserved urine output, but oliguria and a rapidly progressive course of AKI can be seen (14). The differential diagnosis of AKI in this setting is fairly broad. For most clinicians, DAIN is low on the list of AKI causes in the absence of "classic" allergic findings such as fever, rash, and eosinophilia.

A wide range of symptoms and signs can accompany the clinical course of DAIN. None is sensitive or specific enough to permit a firm diagnosis, especially because the clinical findings vary widely depending both on the inciting class of medications as well as the individual patient drug response. Most often, a patient with DAIN has few or no clinical symptoms or signs suggestive of this disorder. Unexplained AKI and/or an abnormal urinalysis/urine microscopy in someone exposed to culprit medications are what raise clinical suspicion. When symptoms are present,

they are nonspecific and include anorexia, malaise, myalgias, arthralgias, chills, and flank pain. The classic triad of fever, rash, and eosinophilia, suggestive of hypersensitivity or allergic reaction, is present in only a minority of patients, typically <5%–10% (9,15).

During the course of AIN, fever and skin rash occur at variable rates and highly depend on the class of drug (Table 2). Fever occurs in approximately 30% of patients (9,11); however, it may be absent with medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and non-β-lactams. In contrast, fever occurs in 50%–100% of patients with documented AIN from β-lactams, particularly methicillin (13–17). Fever is either low-grade or intermittently spiking and usually develops within 1 or 2 weeks of drug administration. Skin rash, as with fever, is an inconsistent finding, present in 15%–50% of DAIN cases and more common with agents that cause a hypersensitivity reaction (9,11,18). Rash is typically morbilliform or maculopapular, but severe dermatologic manifestations such as toxic epidermal necrolysis or diffuse erythroderma may occur with drugs such as allopurinol, phenytoin, or sulfa-based agents.

Laboratory Findings. A slowly rising serum creatinine, typically developing within 7–10 days of drug exposure, is common with DAIN. Importantly, the time frame from exposure to AKI can be as short as 1 day with previous β-lactam exposure to as long as many months (NSAIDs, proton-pump inhibitors), depending on the offending drug. Severe AKI requiring renal replacement therapy also occurs (9,11,15,18). Disturbances in renal potassium, sodium, and acid excretion with hyperkalemia, salt wasting, and/or metabolic acidosis provide clues that drug-induced tubulointerstitial injury has developed (18).

Eosinophilia is a classic finding associated with DAIN and should alert healthcare providers to the possibility of a drug hypersensitivity reaction. The prevalence of eosinophilia approaches 80% with β-lactams such as methicillin, but it occurs in no more than one-third of cases with non-β-lactam drugs, making it an insensitive marker (9,15,18). Blood eosinophils may be only modestly elevated (4%–8%) or markedly abnormal (>50%). Increased serum IgE levels are inconsistently reported, whereas an elevated sedimentation rate, reflecting the underlying inflammatory state and anemia, is often seen (9,18).

Whereas urine chemistries (FeNa and FEurea) are not helpful to diagnose DAIN and may be above or below prerenal/ATN cutoffs, urinalysis is an essential test to investigate the possibility of DAIN (15). Proteinuria (1+ to 2+) and positive blood are seen on dipstick testing. In general, hematuria is present in less than half of cases, but is more common (up to 90%) with drugs such as methicillin and other β-lactams. The presence of leukocytes is another common urinary abnormality. In methicillin-associated AIN, pyuria is reported as being nearly universally present. However, in other forms of DAIN, pyuria is noted in <50% of cases (15,18). Fogazzi *et al*. recently described urinary findings in 21 patients with biopsy-proven DAIN (19). On urine microscopy, leukocytes and RBCs were found in only 12 and 9 patients, respectively, confirming the previously reported rates. WBC casts seen on urine microscopy in a patient with AKI without pyelonephritis are highly suggestive of AIN (15,18). Other urinary sediment findings include RTECs, RTEC casts, and granular casts, reflecting tubular injury and necrosis. In the series of Fogazzi *et al*., many hyaline and granular casts (18 of 21) were described in DAIN, further supporting renal tubular injury by the inflammatory process (19). Surprisingly, RBC casts were noted in 6 of 21 patients and WBC casts in only 3 of 21 patients (19). Although our patient had leukocyturia, as well as WBC casts on the second urine examination, clinicians should not mistakenly exclude DAIN as a cause of AKI in the absence of pyuria or WBC casts.

Urinary eosinophils are neither highly sensitive nor specific for diagnosis of DAIN (20–22). Although Hansel stain (versus Wright stain) improves test sensitivity, eosinophiluria remains a test with significant limitations as numerous disease states manifest eosinophiluria in the absence of AIN. Included are cystitis or prostatitis, pyelonephritis, atheroembolic disease, acute tubular necrosis, and rapidly progressive GN, many of which also present with AKI. Combining the studies that examined the utility of eosinophiluria for AIN is suboptimal due to the different definitions used for a positive test (percentage of eosinophils) and the varied gold standards (clinical versus kidney biopsy) utilized. Sensitivity (63%–91%) and specificity (52%–93%) are quite variable, whereas positive and

Table 2. Selected drugs associated with acute interstitial nephritis

Antibiotics
β-lactam drugs[a]
Fluoroquinolones[a]
Rifampin[a]
Sulfa-based drugs[a]
Erythromycin
Chloramphenicol
Vancomycin
Minocycline
Ethambutol
Analgesics
Nonsteroidal anti-inflammatory drugs[a]
Selective cyclooxygenase-2 inhibitors
Antiviral medications
Acyclovir
Abacavir
Indinavir
Atazanavir
Gastrointestinal medications
Proton-pump inhibitors[a]
Histamine-2 receptor blockers
Anticonvulsants
Phenobarbital
Phenytoin[a]
Carbamazepine
Other
Allopurinol[a]
5-Aminosalicylates[a]
Antiangiogenesis drugs (tyrosine kinase inhibitors)
Diuretics
Captopril
IFN
Cyclosporine

[a]Most common offending agents.

negative predictive values range widely from 38% to 50% and from 74% to 93%, respectively (5). Our patient did not have eosinophiluria despite severe DAIN with numerous eosinophils on kidney biopsy, supporting the limited value of the test.

Histopathology. Kidney biopsy definitively establishes a diagnosis of DAIN; interstitial inflammation and tubulitis are the main pathologic findings. A predominance of lymphocytes and monocytes, often accompanied by eosinophils, plasma cells, neutrophils, and histiocytes, comprise the interstitial infiltrate. In DAIN secondary to NSAIDs or β-lactam antibiotics, the mononuclear component of the infiltrates is primarily composed of T cells, followed by monocytes and B cells (23). A significant component of interstitial eosinophils suggests DAIN, whereas neutrophils support bacterial infection. However, all cell types may be encountered in DAIN and eosinophils are not identified in all cases, especially when NSAIDs are the offending agent.

DAIN is also characterized by tubulitis, a process whereby inflammatory cells insinuate through the tubular epithelium. Tubular injury associated with tubulitis manifests as irregular luminal contours, luminal ectasia, cytoplasmic simplification, loss of brush border, and apoptosis. Early interstitial edema associated with DAIN may evolve into chronic interstitial fibrosis with irreversible tubular atrophy. At times, the interstitial infiltrate seen with DAIN may contain epithelioid histiocytes, which form noncaseating granulomas. These findings are indistinguishable from those seen with sarcoidosis. Glomeruli and blood vessels are generally spared.

Diagnosis. The diagnosis of DAIN should be entertained in any patient with clinical manifestations of a hypersensitivity reaction and history of exposure to any culprit drug (15–18). Although skin rash, peripheral eosinophilia, eosinophiluria, and sterile pyuria are suggestive, they are insufficient to confirm the diagnosis (11,14,15,18). Importantly, as seen in our patient, absence of these findings (except pyuria) does not exclude the diagnosis. Thus, DAIN should be considered in all patients with unexplained AKI who were recently exposed to a potential offending agent.

Ultrasonography and computed tomography scanning typically demonstrate bilateral kidney enlargement and diffuse cortical hyperechogenicity (24), related to inflammatory cell infiltration and edema. These findings are neither sensitive nor specific for AIN, and are primarily useful to rule out urinary tract obstruction. Renal scanning with ^{67}Ga scintigraphy is also not sufficiently sensitive or specific to establish or exclude the diagnosis of AIN (25,26). The main benefit of ^{67}Ga scintigraphy may be in differentiating DAIN from ATN, which usually yields a negative result, making it a potentially useful test in situations in which renal biopsy is contraindicated. Positron emission tomography scanning has recently gained attention as another noninvasive imaging test to diagnose AIN; however, the optimistic initial results need to be verified by others (27). Ultimately, kidney biopsy is usually required to clinch the diagnosis in most cases that are not clinically obvious. However, in circumstances where kidney biopsy is contraindicated due to excessive risk or the patient refuses kidney biopsy, where steroids can be safely administered to the patient, and where DAIN is very likely the cause of AKI, a trial of empirical steroids can be given if culprit drug withdrawal has not improved kidney function.

Management. Discontinuation of the offending medication is the mainstay of treatment of DAIN. This is often challenging in patients receiving multiple drugs that could be reasonably considered for causing the AIN. A careful review of the timing of exposure and clinical and laboratory manifestations may point to the culprit. For example, rash and eosinophilia may point to a sulfonamide, β-lactam antibiotic, or phenytoin. Full or partial recovery of kidney function generally occurs if DAIN is recognized early and the offending agent is withdrawn quickly, preferably as soon as DAIN is diagnosed. Probability of recovery is highly dependent on the duration of kidney injury before diagnosis because irreversible interstitial fibrosis begins to develop at 14–21 days. Unfortunately, a significant number of patients develop CKD (11).

Because DAIN is an allergic, inflammatory process, use of immunosuppressive agents such as corticosteroids for treatment is attractive. Case series and small retrospective studies suggest that corticosteroid therapy may be beneficial in some patients, but there are no prospective, randomized controlled trials to verify efficacy. The benefits reported are quicker renal recovery with increased chance of reaching baseline kidney function, but these beneficial steroid effects are not noted in all studies (7,15,28,29). Two retrospective studies evaluating steroid therapy for AIN reached discordant conclusions. In one study, 67 patients with biopsy-proven AIN (92% drug induced) who received steroids or standard care had their kidney function assessed after 12 months (9). The steroid regimen varied based on nephrologist preference, but a typical regimen included 500 mg of intravenous methylprednisolone for 2–4 days followed by oral prednisone (0.75 mg/kg) tapered over 3 weeks. In the 42 patients with complete data, no difference was noted in serum creatinine concentration between the two groups at 1, 6, and 12 months; only 2 of 35 patients were dialysis dependent. However, stage 3 CKD with a mean serum creatinine of 1.6 mg/dl developed in a significant number of patients. In contrast, a beneficial effect of steroids was noted in another study of patients with biopsy-proven DAIN (30). Among 61 patients with DAIN, 52 were treated with intravenous steroids (methylprednisolone pulse doses ranging from 250 to 500 mg) for 3–4 days followed by 1 mg/kg of oral prednisone tapered over 8–12 weeks. Patients given steroids had better kidney function at mean 19 months follow-up (2.1 mg/dl versus 3.7 mg/dl; $P<0.05$). Two steroid-treated patients were dialysis dependent (3.8%) compared with four of nine patients (44.4%) treated conservatively. Steroid therapy within 7–14 days of diagnosis and less interstitial fibrosis were associated with improved renal recovery.

Acknowledging the limitations of corticosteroids in DAIN, a reasonable approach that I utilize to potentially improve outcomes includes the following: (*1*) DAIN should be considered in a patient with unexplained AKI exposed to culprit drugs and the offending medication(s) discontinued; (*2*) kidney function should be monitored after drug withdrawal, and kidney biopsy considered if there is no improvement within 5–7 days; (*3*) a trial of steroids may be warranted (as described above) if the

duration of AKI is <3 weeks, minimal interstitial fibrosis is present on biopsy, and no major contraindications exist; (*4*) if kidney function improves, steroids should be continued for 4–6 weeks, and then tapered over the ensuing 4 weeks; (*5*) steroids should be discontinued if no meaningful improvement in kidney function occurs after 3–4 weeks of therapy; and (*6*) mycophenolate mofetil should be entertained in patients responding to steroids but developing adverse effects or intolerance. In regard to use of steroids, I favor intravenous pulse steroids as I feel this therapy rapidly quells the inflammatory reaction, although definitive clinical data to support this approach are lacking.

With regard to the patient in this case presentation, piperacillin/tazobactam was discontinued and vancomycin alone was used to treat her MRSA infection. Despite this, kidney function continued to decline with serum creatinine increasing to 6.62 mg/dl. Because the infection was resolving and the patient had no major contraindications to steroids, 250 mg of intravenous methylprednisolone was administered daily for 3 days followed by 60 mg of oral prednisone daily. Serum creatinine peaked at 7.21 after 3 days of steroids and kidney function subsequently improved with serum creatinine 1.52 on discharge (day 22) from the hospital (Table 1).

Drug-induced AIN is common and must be considered in the differential diagnosis when patients develop hospital-acquired AKI. The clinical presentation and laboratory findings vary with causative agents. Quite commonly, no systemic evidence of a hypersensitivity reaction is present. A high index of suspicion and early definitive diagnosis with kidney biopsy is required. Although the mainstay of therapy for DAIN is discontinuation of the offending agent, adjunctive steroid therapy is often necessary in my clinical experience. Steroids appear to decrease the duration of AKI in some patients and may be associated with more complete renal recovery if utilized early after diagnosis.

Final Diagnosis. Dr. Randy Luciano, Senior Yale Nephrology Fellow. Hospital-acquired AKI in this patient was due to drug-induced AIN. In the patient presented, a second viewing of the urine sediment demonstrated white cell casts. How common are WBC casts in other forms of AKI and are urinary white cell casts sufficient for diagnosis and treatment with steroids, or would you always recommend biopsy confirmation?

Dr. Perazella. WBC casts are not specific for AIN. They may be seen in other infectious or inflammatory disorders of the kidney such as acute pyelonephritis, acute papillary necrosis, or acute GN. Typically, pyelonephritis and papillary necrosis are clinically obvious, whereas differentiating AIN from acute GN can be difficult. At times, the urine sediment in acute GN has mixed RBC and WBC casts. But, as noted in the DAIN series of Fogazzi *et al.*, 6 of 21 patients had RBC casts. Applying this information to empirical steroid therapy for presumed AIN is tricky. Often, clinicians want to make a diagnosis using the least invasive test available—for AIN, noninvasive tests such as urine eosinophils/urine microscopy, gallium scan, and, more recently, positron emission tomography are utilized. Unfortunately, they are not suitably sensitive or specific for AIN to be recommended. In general, a kidney biopsy is required, however, as I noted in the discussion, cases must be individualized putting together the likelihood of diagnosis, as well as the risks and benefits of kidney biopsy and patient exposure to steroids.

Dr. Steven Coca, Yale Nephrology Faculty. Novel urinary biomarkers are being utilized to diagnose various forms of AKI. Are there any urinary biomarkers that may be used to noninvasively detect AIN?

Dr. Perazella. This area has not been studied to any great extent. Many years ago, a test known as "urine major basic protein" was probably the first urinary biomarker utilized in AIN. The rationale for this test was that major basic proteins were present in granules within eosinophils and released from both intact and lysed cells in the urine of patients with AIN. The hope was that this test would improve sensitivity (above urine eosinophils), but never caught on as the specificity problem remained. Recently, a study examined several urinary biomarkers in 40 patients with biopsy-proven DAIN (31). In this study, urinary monocyte chemotactic protein-1 (MCP-1) levels showed the closest correlations with interstitial edema and inflammatory infiltration, important histopathologic findings in the acute phase of AIN. Because MCP-1 is a potent chemoattractant and activating factor for monocytes (one of the inflammatory cells present in AIN), urinary MCP-1 level likely reflects the degree of interstitial monocyte infiltration and the acute response of RTECs. It remains to be seen if these data are replicated by others and if this noninvasive test can accurately predict DAIN and those who might benefit from immunosuppressive therapy.

Dr. Ursula Brewster, Yale Nephrology Faculty. How does a pharmacologic agent trigger the immune-mediated injury in DAIN?

Dr. Perazella. Immunologic injury induced by medications as the cause of DAIN is supported by the low frequency of occurrence, the absence of dose dependency, occasional associated "allergic" symptoms/signs, and rapid recurrence with repeat drug exposure. Drugs cause AIN primarily by acting as exogenous antigens, which can be directly trapped within the interstitium or circulate as an immune complex that subsequently deposits within the interstitium. Alternatively, drug antigens can bind to tubular antigens and act as haptens or perform molecular mimicry of the tubules and/or interstitium. Although both cell-mediated and humoral immunity are involved in this process, injury is initiated when an antigen-processing lymphocyte is activated by the aforementioned antigens. This results in the formation of activated T cells that promote differentiation and proliferation of other T cells. The resulting interstitial inflammatory infiltrate, which produces a variety of cytokines and chemokines including TGF-β, PDGF-β, EGF-β, and fibroblast growth factor-2, promotes tubulointerstitial injury and cytotoxicity. Over time, tubulointerstitial inflammation and edema transition to fibrosis and tubular loss—perhaps due to fibroblast-induced epithelial-to-mesenchymal transition.

Disclosures

None.

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Published online ahead of print. Publication date available at www.cjasn.org.