Clinical Approach to Diagnosing Acute and Chronic Tubulointerstitial Disease

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Tubulointerstitial diseases are a relatively common cause of acute and/or chronic kidney disease. Acute tubulointerstitial nephritis (ATIN) most commonly develops in patients exposed to various medications; however, it can occur from infections, autoimmune and systemic diseases, environmental exposures, and some idiopathic causes. Chronic tubulointerstitial nephritis may develop in patients with previous ATIN or may be the initial manifestation of an autoimmune, systemic, environmental, or metabolic process. It can be challenging for clinicians to differentiate the various causes of acute and chronic kidney disease. In particular, distinguishing ATIN from other causes of acute kidney injury, such as acute tubular necrosis or a rapidly progressive glomerulonephritis, is important as treatment and prognosis are often quite different. To this end, clinicians use clinical assessment, certain laboratory data, and various imaging tests to make a diagnosis. Unfortunately, most of these tests are insufficient for this purpose. As a result, kidney biopsy is often required to accurately diagnose ATIN and guide management. For chronic tubulointerstitial nephritis, kidney biopsy is needed less often as available therapies for this entity, with a few exceptions, are limited and primarily supportive.

Key Words: Tubulointerstitial disease, Acute kidney injury, Acute tubulointerstitial nephritis, Chronic tubulointerstitial nephritis, Urine microscopy

INTRODUCTION

Tubulointerstitial diseases are a relatively common cause of both acute kidney injury (AKI) and chronic kidney disease (CKD). As listed in Table 1, there are several acute and chronic causes of tubulointerstitial nephritis. Overwhelmingly, drugs are the most common cause of acute tubulointerstitial nephritis (ATIN) in developed countries, followed by infection, autoimmune and systemic disorders, and metabolic etiologies.[1] For chronic tubulointerstitial nephritis (CTIN), there are a number of causes, many which overlap with ATIN.[2,3] As a partial list, some of the etiologies associated with CTIN include classic tubulointerstitial diseases, such as Sarcoidosis, Sjogren's syndrome, metabolic disorders, IgG4 tubulointerstitial disease, and nephrotoxins.[2,3] My focus will be primarily on the diagnostic evaluation of ATIN; however, this review will also briefly touch on the evaluation of CTIN.

Before discussing the diagnostic approach to ATIN, it is worth briefly mentioning the typical textbook approach to differentiating tubulointerstitial nephritis from glomerular diseases (nephritic and nephrotic syndromes) and tubular injury. As seen in Table 2, the basic textbook approach suggests a fairly easy differentiation of the various kidney processes; however, the reality is that there is significant overlap. These discrepancies will be discussed for the reader.

ACUTE TUBULOINTERSTITIAL NEPHRITIS

Clinicians frequently encounter patients with AKI admitted to the general hospital wards and the medical and surgical intensive care units.[4] Although the majority of hospital-acquired AKI is because of either prerenal AKI or acute tubular necrosis (ATN), ATIN is not an uncommon cause in this setting. In fact, biopsy-proved ATIN is diagnosed in approximately 10%-27% of patients without an obvious cause of AKI.[5-9] In view of this, clinicians must be skilled in the diagnostic evaluation of AKI to be able to differentiate these various entities and provide appropriate therapy. Importantly, the prevalence of ATIN, likely driven by drugs, also appears to be an increasing cause of hospital-acquired AKI.[9] Because ATIN appears to be on the rise and data suggest that early recognition and treatment matter, diagnostic acumen becomes all the more important to salvage kidney tissue by reducing the amount of tubulointerstitial fibrosis that may ultimately develop.[1,10]

In differentiating ATIN from other causes of AKI, a variety of clinical tools are used by clinicians including a focused history, physical examination, imaging tests, and certain laboratory data. Clinical history and examination are extremely important; however, additional diagnostic tests are often required. Imaging modalities, such as kidney ultrasonography and computed tomography (CT) scan are often ordered, whereas gallium scanning and more recently positron emission tomography (PET) scan are used in some cases. Serum tests are generally not helpful, whereas urinary tests (urine dipstick, urine microscopy, urine chemistries, and eosinophiluria) are commonly used in the hope of differentiating ATIN from other causes of hospital-acquired AKI. Ultimately, kidney biopsy is required to accurately make a diagnosis and guide therapy in those with ATIN.

Clinical Assessment

Critical in the initial clinical evaluation of the patient where ATIN is considered part of the differential diagnosis is determining whether a systemic process is present or if there was exposure to a suspect drug. Most times, diseases such as Sarcoidosis (pulmonary disease, eye, skin, and neurologic involvement, hypercalcemia/hypercalciuria, and nephrolithiasis) and Sjogren's syndrome (Sicca syndrome) have extrarenal manifestations. Tubulointerstitial nephritis with

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uveitis may be recognized when a young patient presents with AKI and eye findings consistent with uveitis. IgG4 disease often involves multiple organs (pancreas, lungs, salivary glands, etc.) and makes diagnosis of kidney involvement less tricky.[2,3] Kidney involvement may be in the form of diffuse disease or masses. However, kidney-limited disease is more difficult to diagnose and requires more directed testing. In regard to medications, any number of agents may cause ATIN; however, common agents include certain antimicrobial agents (β-lactams, sulfonamides, quinolones, and antiviral agents), anti-ulcer agents (proton pump inhibitors, H_2-antagonists), nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, allopurinol, and some of the newer agents, such as the anti-angiogenesis agents and the immune checkpoint inhibitors.[1,10,11] One must not forget environmental exposure to heavy metals and other nephrotoxins.

In general, nonspecific symptoms are observed with ATIN,[1,10] including generalized malaise, fatigue, weakness, and anorexia. Myalgias and arthralgias, flank pain, and "fever" may also develop. Depending on the etiology or the drug class involved, patient may describe a pruritic skin rash, which should raise suspicion for an allergic or drug-related process. Unfortunately, none of these symptoms are particularly specific to ATIN and may be seen with any number of clinical conditions.

As with clinical symptoms, physical examination findings are not always helpful and in truth are often not present. Some findings that can suggest ATIN are a low grade or spiking fever occurring in the absence of documented infection. This can signal a systemic disease associated with ATIN (sarcoidosis, HIV infection, and certain microbial agents) or a "drug fever" with associated ATIN. However, fever is not present in the majority of patient with this kidney lesion, although it commonly occurs with ATIN from methicillin and other penicillin derivatives.[7-18]

An examination finding that can be helpful to the clinician in pointing to drug-induced ATIN is a classic drug eruption, typically morbilliform and involving the trunk. However, as with other examination findings, it is not a sensitive finding and is often not present even in the setting of a very severe ATIN. The literature notes that drug rash is observed in 15%-50% of ATIN cases, is more likely with drugs that cause hypersensitivity reactions (β-lactams, sulfonamides, phenytoin), and is rarely seen (or completely absent) with certain classes of drugs, such as NSAIDs and proton pump inhibitors.[7,13,19] A finding almost never encountered on physical examination of patients with ATIN is palpably enlarged, tender kidneys, although they are described in the literature.[1,10] In the end, outside classic systemic disease findings (sarcoidosis and others), noninfection associated fever and classic drug skin eruption; it is difficult to raise ATIN to the top of the differential for AKI in the absence of other supportive data.

CLINICAL SUMMARY

- Tubulointerstitial diseases are a relatively common cause of both acute and chronic kidney disease.
- Drugs are the most common cause of acute tubulointerstitial nephritis; however, other causes include autoimmune and systemic disorders, infections, and metabolic etiologies.
- Chronic tubulointerstitial nephritis may develop chronically following the development of acute tubulointerstitial nephritis or may be the initial manifestation of an autoimmune or systemic process.
- Clinical and laboratory findings (blood, urine, and radiologic studies) may raise the possibility of acute tubulointerstitial disease, but kidney biopsy is generally required to make a definitive diagnosis.

Blood Testing

Very few blood tests are helpful in moving the differential diagnosis of AKI toward ATIN with the exception of serum eosinophilia. Serum eosinophils may be only modestly elevated or markedly abnormal, at times making up 50%-75% of the total white blood cell count.[18] This blood test is most helpful in raising the specter of drug-induced ATIN as significant eosinophilia often reflects a severe allergic drug reaction.[1,10] Eosinophilia also occurs in other AKI settings, such as eosinophilic leukemia, cholesterol emboli syndrome, vasculitis, and malignancy; however, these systemic processes are often clinically recognizable by other clinical manifestations.[1,10] Sadly, as with other tests used to evaluate for the possibility of ATIN, eosinophilia is not a sensitive finding. As with fever and rash, significant eosinophilia in ATIN is more common with certain drug classes and may be absent despite the presence of an eosinophil-dominant inflammatory infiltrate on kidney biopsy.[7,16,19]

Anemia is described as a common laboratory finding associated with ATIN. However, it is quite nonspecific and widely prevalent in many patients, especially those with AKI alone or superimposed on CKD.[8] The pathophysiology of anemia likely involves a number of processes including reduced erythropoietin synthesis from kidney injury and erythropoietin hyporesponsiveness from underlying inflammation and/or infection.[8] Although erythrocyte sedimentation rate and C-reactive protein may also be elevated with ATIN, they are very nonspecific findings and generally unhelpful.[8,19]

Liver function tests may also be abnormal with ATIN, but this typically signals an associated drug-induced hepatitis. Nonetheless, this is a rare and quite nonspecific finding. The seasoned nephrologist may observe the presence of hyperkalemia and a hyperchloremic metabolic acidosis that is out of proportion to the degree of AKI, raising suspicion for associated tubulointerstitial injury.[19] Other patterns of tubulointerstitial injury, such as a Fanconi syndrome, salt-wasting nephropathy, distal renal tubular acidosis, and urinary concentrating defects are described with ATIN.[18]

Urinalysis and Urine Microscopy

One of the most commonly used diagnostic tests used to assess AKI is the central laboratory automated urinalysis.