Pathologic Perspectives on Acute Tubular Injury Assessment in the Kidney Biopsy

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Summary: The molecular mechanisms in acute tubular injury (ATI) are complex and enigmatic. Moreover, we currently lack validated tissue injury markers that can be integrated into the kidney biopsy analysis to guide nephrologists in their patient's management of AKI. Although recognizing the ATI lesion by light microscopy is fairly straightforward, the staging of tubular lesions in the context of clinical time course and etiologic mechanism currently is not adapted to the renal pathology practice. To the clinician, the exact time point when an ischemic or toxic injury has occurred often is not known and cannot be discerned from the review of the biopsy sample. Moreover, the assessment of the different types of organized necrosis as the underlying cell death mechanism, which can be targeted using specific inhibitors, has not yet reached clinical practice. The renal pathology laboratory is uniquely qualified to assess the time course and etiology of ATI using established analytic techniques, such as immunohistochemistry and electron microscopy. Recent advances in the understanding of pathophysiological mechanisms of ATI and the important role that certain types of tubular cell organelles play in different stages of the ATI lesions may allow differentiation of early versus late ATI. Furthermore, the determination of respective cell injury pathways may help to differentiate ischemic versus toxic etiology in a reliable fashion. In the future, such a kidney biopsy–based classification system of ATI could guide the nephrologist's management of patients in regard to treatment modality and drug choice.
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Despite detailed classification of acute renal failure and identification of several damage mechanisms, the understanding of acute tubular injury (ATI) and its diagnosis according to respective injury etiology still is incomplete.[1] The term *ATI* should be reserved for the clinical pathologic entity of intrinsic renal failure that is the result of either ischemic or toxic insult to the kidney with evidence of tubular injury such as altered fractional excretion of sodium or specific tubular injury markers, when other causes have been excluded.[2] The percentage of cases of acute kidney injury (AKI) that can be attributed to acute tubular injury/necrosis are difficult to ascertain, but the condition likely is responsible for the majority of cases of AKI that require renal replacement therapy. The term *acute tubular necrosis* itself is a misnomer because necrosis, although a feature in animal models, is only one morphologic manifestation of clinical ATI. Moreover, the morphologic evidence of frank tubular necrosis is not a frequent finding in kidney biopsy specimens obtained in the context of clinical AKI.

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HISTOLOGIC MANIFESTATIONS OF ACUTE TUBULAR CELL INJURY

The lesions in both ischemic and toxic ATI primarily involve the tubules and spare the glomeruli.[3] Unfortunately, tubular epithelial cell death is not always evident by light microscopy.[4] Morphologic changes often are more subtle in ischemic injury while more obvious cytopathologic changes are seen in the toxic form. Moreover, the sites of tubular damage differ between the various forms of injury. In the ischemic form, tubular injury is patchy, affecting short stretches of the proximal straight tubule and focal areas of the ascending limb of the loop of Henle. In the toxic form, tubular injury is more continuous along all segments of the proximal tubule. Moreover, the degree of involvement of different segments may vary with specific toxins.

Ischemic ATI

The histological manifestation of ATI varies with the severity of renal failure and the evolution of the lesion. Early in the course cell changes may vary from minimal alteration to severe cell swelling (Fig. 1A). Associated with the injury, both shedding of viable and necrotic cells into the tubular lumen may be seen (Fig. 1B). In sections stained with periodic acid-Schiff, thinning or absence of the brush border of the proximal tubule often is seen (Fig. 1C). Hyaline, granular, cellular, and/or pigmented casts are seen in the distal portion of the nephron, and often are particularly

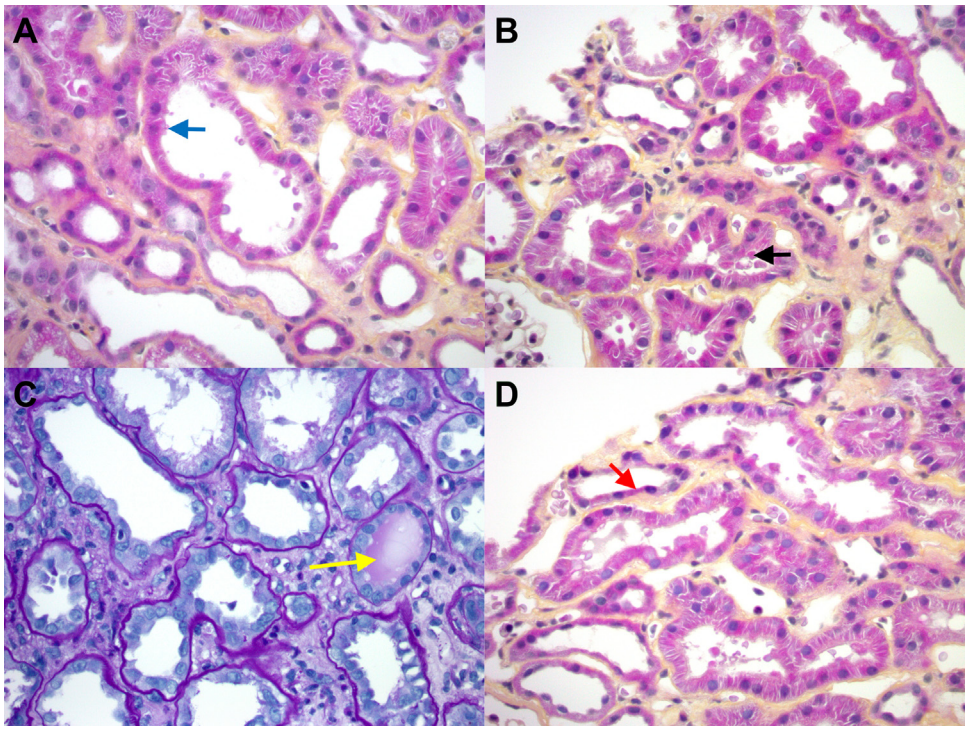

Figure 1. Histopathology of ATI. (A) Early changes in ATI include cell swelling (blue arrow) and apical blebbing (Hematoxylin Phloxine Saffron [HPS] stain, 400x). (B) Sloughing of individual epithelial cells (black arrow) (HPS, 400×). (C) Tubular casts with Tamm-Horsfall protein (yellow arrow) (periodic acid-Schiff, 400×). (D) Tubular cell regeneration with flattened epithelial cells and hyperchromatic nuclei (red arrow) (HPS, 400×).

prominent in the collecting ducts. These casts consist of Tamm-Horsfall protein mixed in with cell debris.[5] As the lesion progresses after initial injury, histologic indicators of cell proliferation, such as mitosis, hyperchromatic nuclei, and a high nuclear-cytoplasmic ratio are seen (Fig. 1D). Most injured tubule cells may be replaced through extensive proliferation of neighboring cells, which may be the predominant mechanism of tubular cell injury repair.[6]

Toxic ATI

Toxic tubular injury has been associated with extensive epithelial injury, which tends to show widespread involvement along all proximal tubular nephron segments.[7] Swelling and vacuolization of proximal tubules with pale enlarged epithelial cells with cytoplasmic vacuolization may be seen.[8] In gold-induced ATI, gold particles may be seen in the cytoplasm of proximal tubules.[9] Extensive calcifications in proximal tubule cells have been described in toxicity caused by amphotericin or bacitracin.[10] Extensive coagulative necrosis has been seen in cases of mercuric chloride poisoning or in cases of poisoning resulting from chemicals such as diethylene glycol.[11] Tubular casts, which may include cell debris, often are seen in toxic ATI. Anesthetic agents, such as methoxyflurane and halothane, and antiretroviral agents such as indinavir, may produce tubular crystalline deposits, which may lead to mechanical obstruction and tubular injury.[12] Uric acid lithiasis and tubular obstruction have been described in patients treated with phenylbutazone.[13]

PATHOPHYSIOLOGICAL MECHANISMS OF ACUTE TUBULAR CELL INJURY

Ischemic ATI

The alterations in cellular metabolism underlying ischemic injury in the kidney are similar to those in other organs. A reduction in oxygen delivery to metabolically active tubular epithelial cells reduces oxidative metabolism and depletes cell stores of high-energy phosphate components. Reperfusion with the return of oxygen delivery enhances generation of oxygen radicals with resultant damage to cell organelles such as mitochondria. Defects in cellular polarity and cytoskeleton assembly occur as a consequence of ischemia. Ischemic injury leads to damage of proteins involved in maintenance of proteins that provide integrity of polarity and cell-to-cell contact, such as E-cadherin, β-catenin, and integrins.[14,15] After ischemic injury, the depletion in cellular adenosine triphosphate stores leads to disruption of the actin cytoskeleton and conversion of polymeric filamentous actin to monomeric G-actin with redistribution of residual F-actin from the membrane surface to a perinuclear location.[16] Reactive oxygen species (ROS) generated by