Acute and Chronic Toxic Nephropathies

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ABSTRACT

Toxic nephropathies manifest morphologically as glomerulonephritides, vasculitides, tubular necrosis, and acute or chronic tubulointerstitial disease. The most common toxicity is acute interstitial nephritis owing to hypersensitivity. However, focal segmental glomerulosclerosis and necrotizing angiitis secondary to heroin abuse, membranous glomerulopathy owing to gold, penicillamine and captopril, thrombotic microangiopathy associated with mitomycin and tubular necrosis owing to cyclosporine A, cisplatin, aminoglycosides, and cephalosporins are also reviewed. The mechanisms of toxicity are poorly understood in most cases, but hypotheses related to cyclosporine A, cisplatin, gold, aminoglycosides, cephalosporins, intravenous narcotics, sulfonamides, and methotrexate are summarized.

Toxic Nephropathies

The spectrum of toxic nephropathies ranges from glomerulonephritis to chronic tubulointerstitial disease and involves a list of drugs from antibiotics to drugs of abuse. This review will cover the major morphologic patterns of injury and will highlight some of the purported mechanisms of injury.

Glomerular injury is most commonly seen with drugs of abuse. Virtually all types of glomerulonephritis have been reported, but heroin associated nephropathy is usually characterized by focal, segmental glomerulosclerosis. Both IgM and C₃ are frequently identified within the abnormal segments; foot process fusion is present by electron microscopic evaluation. Most patients present with the nephrotic syndrome and exhibit a relentless course. At least two mechanisms of injury have been postulated: (1) the narcotic serves as a hapten to stimulate immune complex formation on a chronic basis, or (2) the narcotic causes increased glomerular capillary permeability which in turn causes the focal lesions. It is interesting that the most common renal lesion in AIDS patients is also focal segmental glomerulosclerosis. The differences between these two glomeruloscleroses are subtle.

Membranous glomerulonephritis is seen with gold, penicillamine, and captopril (figure 1). The morphologic findings are similar to those of idiopathic membranous glomerulonephritis, but the renal dysfunction resolves upon withdrawal of the drug. Although
Figure 1. The glomerulus exhibits typical features of membranous glomerulonephritis which may be associated with gold, penicillamine, and captopril. (H&E mag 25×)

Figure 2. Tubular necrosis accompanied by dense interstitial lymphocytic infiltrates characterizes cyclosporine toxicity (H&E mag 50×).
immune complexes are identified along the glomerular basement membrane, neither the drugs nor their metabolites can be isolated from these complexes. Gold can be detected by electron microscopy in the proximal convoluted tubules. In at least one experimental model, circulating renal tubular antibodies have developed concomitantly with the morphologic occurrence of tubulointerstitial disease after gold injection. Renal tubular antigens can also be identified in mesangial and subendothelial deposits. Thus, gold and other drugs eliciting a membranous glomerulonephritis may release antigens from the kidney or other sites which provoke immune complex deposition. Focal proliferative and necrotizing glomerulonephritis may be provoked by penicillin, allopurinol, or thiazides. It is probably due to hypersensitivity.

Two types of vascular lesions have been attributed to drug toxicity. Patients who abuse either hallucinogens or narcotics may develop severe necrotizing angiitis resembling polyarteritis nodosa. Thrombotic microangiopathy with endothelial cell proliferation and fibrin deposition has been reported with the use of mitomycin and cis-diaminedichloroplatinum II (cis-platin). The mechanisms of injury are unknown although direct toxicity, and immune complex mediated effects have been postulated.

Tubular damage is caused by aminoglycosides, cephalosporins, and heavy metals including cis-platin, sulfonamides, and methotrexate. These agents cause acute tubular necrosis (figure 2). The mechanism of aminoglycoside toxicity has been extensively studied. Aminoglycosides are low molecular weight, highly water soluble, polycations which bind to the brush border of the proximal convoluted tubular cells. The aminoglycosides undergo pinocytosis and fusion with lysosomes. In the acid pH of the lysosome the drug binds to phospholipids impairing the activity of phospholipases and resulting in the accumulation of myeloid bodies, lysosomal rupture, and cell death. Nephrotoxicity is related to the degree of renal uptake of the drug and increases with the number of free amino groups.

Cephalosporins are absorbed into the proximal convoluted tubular cells from the antiluminal surface and diffuse across the cell to the lumen. The rate of diffusion affects the intracellular concentration and the toxicity. Cephaloridine is particularly toxic owing to the development of high intracellular concentrations. One of the recently proposed mechanisms of cellular injury by cephalosporins is that the drug undergoes a redox reaction to form superoxide radicals which react with lipids to form hydroperoxides. These in turn inhibit gluconeogenesis with subsequent impairment of organic ion transport across the cell membrane eventually resulting in cell death.

Cisplatin, a highly effective chemotherapeutic agent in a variety of tumor types (figure 3) causes severe nephrotoxicity with necrosis in the proximal convoluted tubule. At least two mechanisms are implicated: (1) reduced renal blood flow and glomerular filtration rate perhaps owing to increased preglomerular vascular resistance, and (2) free radical production within the proximal convoluted tubular epithelium. Platinum can be identified on x-ray analysis of ultrathin sections in the microbodies of tubular epithelium and radical scavengers can ameliorate the necrosis, implying a mechanism similar to that invoked in cephalosporin toxicity.

Both sulfonamides and methotrexate may precipitate in renal tubules causing an obstructive uropathy. Adequate hydration and selection of the patient can prevent this toxicity.
TOXIC NEPHROPATHIES

Figure 3. The small arteriole exhibits infiltration by lymphocytes and endothelial nuclear enlargement consistent with the vasculitis seen in cis-platin toxicity (H&E mag 50×).

Figure 4. Acute interstitial nephritis is the most common form of nephrotoxicity (H&E mag 50×).
Acute tubulointerstitial disease or acute interstitial nephritis is the most common drug toxicity reported in the literature (figure 4). The histologic picture is that of interstitial edema and chronic inflammation involving areas of tubular degeneration or necrosis. Numerous drugs have been implicated including penicillins, sulfonamides, allopurinol, diuretics, and non-steroidal antiinflammatory agents (NSAIDS). In the majority of these cases, hypersensitivity to the drug is invoked; the reaction is not dose-related and may recur with reintroduction of the drug. Although the morphologic features of cyclosporine A toxicity also include an interstitial infiltrate of lymphocytes and tubular necrosis, hypersensitivity has not been proven as a mechanism of injury. Instead, attention has been paid to tubular injury owing to the cytochrome P450 system to generate a toxic metabolite, or hypoxia from decreased blood flow by intrarenal arteriolar vasoconstriction or by hemodynamic alterations involving the renin-angiotensin-aldosterone or prostaglandin systems.

Chronic tubulointerstitial disease is most commonly caused by analgesic nephropathy with aspirin and phenacetin implicated together. Medullary injury with papillary necrosis and sclerosis comprise the morphologic findings.

Nephrotoxicity owing to drugs is a heterogeneous group of lesions involving all portions of the kidney. Although acute tubulointerstitial disease, "allergic interstitial nephritis", owing to hypersensitivity is the most common drug-induced renal lesion, acute tubular necrosis, vasculitis, and glomerulonephritides have all been linked to specific drugs through a wide variety of mechanisms.

References