Review Article

Drug-induced Kidney Disease – Pathology and Current Concepts

Alwin HL Loh,[1] *MBChB(Hons), FRCPath*, Arthur H Cohen,[2,3] *MD*

Abstract

The kidneys can be damaged by a large number of therapeutic agents. The aim of this article is to discuss the pathological features of drug-induced renal disease as diagnosed by kidney biopsy. The literature is reviewed and cases seen by the authors that have a known drug association are analysed. Mechanisms of injury are varied and all renal structures may be affected. The tubulointerstitial compartment is most frequently involved, but glomerular and vascular lesions are seen in a significant proportion of cases.

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Key words: Drug, Kidney, Nephrotoxicity, Pathology

Introduction

Departing from the usual account of drug-induced renal disease according to the specific type of drug, we divide this discussion into 3 main areas - glomerular injury, vascular injury and tubulointerstitial changes. In doing so, more emphasis will be placed on morphological findings although functional toxicity (with little or no structural abnormalities detected by routine techniques) plays an equally important role in certain classes of drugs. After diabetes mellitus and hypertension, glomerulonephritis, autosomal dominant polycystic kidney disease and interstitial nephritis account for most of the causes of chronic kidney disease in the United States and other developed countries.[1] In the United States Renal Data System 2006 Annual Data Report, "analgesic abuse" and "nephropathy/other agents" were the only 2 primary diagnoses that specifically classify drugs or chemicals as being the causes of end-stage renal disease (ESRD). The true incidence of drug-induced acute and chronic interstitial nephritis is probably underestimated as interstitial nephritis is a non-specific finding in chronically scarred kidneys. Furthermore, the tubulointerstitium is not the only renal compartment involved with this type of injury.

The human kidneys together account for less than 1% of body weight, yet receive about 20% of the cardiac output. They are primarily involved in filtering and concentrating various substances and chemical agents. These substances may reach high concentrations in the kidney and become toxic. Depending on the segment of the nephron targeted, different morphological changes are detected in the renal biopsy, which remains the gold standard for documenting kidney disease. The mechanisms for glomerular, vascular and tubulointerstitial injuries are summarised in Tables 1 to 3.

Glomerular Injury

The glomerulus is a specialised structure which is composed of cells (epithelial, mesangial, endothelial) and matrix (mesangium, basement membrane) in a complex network of capillaries. Injury to these various components of the glomerulus produces more specific clinical syndromes than diseases affecting the extra-glomerular vasculature, tubules and interstitium. For example, podocyte (visceral epithelial cell) injury leads to nephrotic syndrome, capillary basement membrane alterations manifest as haematuria with or without proteinuria, while more destructive (necrotising/crescentic) acute lesions give rise to the syndrome of rapidly progressive glomerulonephritis. In the mature glomerulus, the podocyte is a terminally differentiated cell which has critical roles in permselectivity, synthesis of the glomerular basement membrane (GBM) and maintaining capillary loop patency.[2] Although we understand a great deal about its ultrastructure, filtration function and molecular phenotype, how certain drugs affect the podocyte remains obscure.[3-7]

[1] Department of Pathology, Singapore General Hospital, Singapore
[2] Cedars-Sinai Medical Center, Los Angeles, USA
[3] David Geffen School of Medicine, University of California, Los Angeles, USA
Address for Correspondence: Dr Alwin H-L Loh, Department of Pathology, Singapore General Hospital, Outram Road, Singapore 169608.
Email: loh.hwai.liang@sgh.com.sg

Table 1. Glomerular Injury

Mechanism	Disease	Drug
Alterations to the renin-angiotensin system/ prostaglandin synthesis	Functional/hemodynamic effect	NSAIDS/CNIs
Podocyte injury, possibly immune (T-cell) mediated	MCD	NSAIDS
Podocyte injury, with phenotypic alterations	FSGS	Pamidronate
Inhibition of lysosomal enzyme	Phospholipidosis	Chloroquine
Immune complex deposition	MGN/Lupus-like glomerulonephritis	Gold/Penicillamine/Hydralazine
ANCA	Crescentic/necrotising glomerulonephritis	Infliximab/Propylthiouracil
Endothelial damage	TMA	CNIs/Bevacizumab

ANCA: antineutrophil cytoplasmic antibody; CNIs: calcineurin inhibitors; FSGS: focal and segmental glomerulosclerosis; MCD: minimal change disease; MGN: membranous glomerulonephritis; NSAIDS: non-steroidal anti-inflammatory drugs; TMA: thrombotic microangiopathy

Table 2. Vascular Injury

Mechanism	Disease	Drug
Endothelial/myocyte damage	TMA	CNIs
Cell or antibody mediated	Inflammatory vasculitis	Various antibiotics
Capillary/ischaemic damage	Analgesic nephropathy	Combination analgesics

CNIs: calcineurin inhibitors; TMA: thrombotic microangiopathy

Table 3. Tubulointerstitial Injury

Mechanism	Disease	Drug
Immune mediated	Acute or chronic tubulointerstitial nephritis	Various antibiotics/NSAIDS
Direct cellular toxicity	ATN/Nephrogenic diabetes insipidus	Cisplatin/Lithium
Changes in osmotic gradient across cell membrane	Osmotic nephrosis	Plasma volume expanders/IVIG
Cast formation obstructing tubules	Tubulointerstitial nephritis/ATN	Various drugs/Sirolimus
Crystal deposition/Calcification	Tubulointerstitial nephritis/ATN/ Nephrocalcinosis	Diethylene glycol/Indinavir/Oral sodium phosphate purgative

ATN: acute tubular necrosis; IVIG: intravenous immune globulin

Podocyte Injury

Minimal change disease (MCD) is a condition characterised ultrastructurally by widespread effacement of podocyte foot processes coupled with normal or near normal findings by light microscopy (LM) and immunofluorescence (IF). The GBM usually has a normal texture and thickness. Accompanying the loss of foot processes is alteration to the filtration slit.[8,9] The extent of effacement may not correlate with the severity of proteinuria[9] contrary to earlier reports. Reconstitution of podocyte foot processes is associated with the improvement of nephrotic syndrome. Non-steroidal anti-inflammatory drugs (NSAIDS), used by millions of people worldwide, are perhaps best known for causing interstitial nephritis (discussed later). Knowledge of an additional important association with MCD came from publications in the 1980s.[10,11] The pathogenic role of T-lymphocytes and interleukins were described in these and a more recent study.[12] Several other medications have been implicated in MCD, including COX-2 inhibitors,[13] the interferons[14,15] and pamidronate[16] (a bisphosphonate). At the functional (physiologic) level, the nephrotoxicity of NSAIDS and COX-2 inhibitors can be explained by their inhibition of renal prostaglandin synthesis, leading to an imbalance of vasodilation and vasoconstrictive forces in favour of the latter.[17] A current case report from the *Case Records of the Massachusetts General Hospital* describes the concurrence of dehydration and the negative effect of ibuprofen on renal blood flow in causing acute tubular necrosis (ATN) as well as glomerular podocyte and endothelial injury.[18] We now know that COX-2 is constitutively expressed in the kidney and its inhibitors show nephrotoxic effects similar to NSAIDS.[19]

A morphologic classification scheme for focal and segmental glomerulosclerosis (FSGS) has been proposed,[20] and they are *NOS* (not otherwise specified), *perihilar*,

cellular, *tip* and *collapsing*. Markowitz and others were the first to report the association between pamidronate and collapsing glomerulopathy.[21-23] This group of patients had received higher than recommended dosages and prolonged courses of the drug. Proteinuria and renal function improved when the drug was withdrawn. Collapsing focal sclerosis is illustrated in Figure 1. In the "idiopathic" form of collapsing glomerulopathy, tubulointerstitial lesions are often a prominent feature in that tubular injury, interstitial inflammation and tubular dilation with proteinaceous casts, akin to those seen in HIV-associated nephropathy (HIVAN), are frequently encountered. These lesions are sometimes out of proportion to the degree of glomerular injury, indicating a pan-nephropathy.[24-26] Thus pamidronate probably has a direct toxic effect on podocytes and epithelial cells lining the nephron.[20] Podocyte phenotypic alterations have been documented in studies involving collapsing glomerulopathy, HIVAN and recurrent FSGS in the allograft.[27-31] In several large series, the proportion of patients who developed ESRD and the rate of progression to ESRD were significantly higher in those with collapsing morphologic features.[24-26,32] Interferon-α, a drug used to treat hepatitis C, can also induce focal segmental glomerulosclerosis and nephrotic syndrome[33-35]; however, the disease itself and ribavirin may be confounding factors in some instances. Sometimes, tubuloreticular inclusions are observed in glomerular endothelial cells with interferon treatment, hence the name "interferon footprints".[36] Another drug linked to FSGS is lithium (see section on tubulointerstitial injury).[37,38]

Chloroquine and the chemically related hydroxychloroquine are anti-malarials used to treat patients with rheumatic disorders and systemic lupus erythematosus. The incidental morphologic consequence of chloroquine usage, in the form of accumulation of lipid inclusions in podocytes, has been known for some time. In 2003, a case describing significant deterioration of renal function due to a high cumulative dose of the drug was described.[39] Since then, a few others have surfaced, confirming the nephrotoxicity (proteinuria) of chloroquine and hydroxychloroquine, reversibility of this toxicity with drug withdrawal, and the close morphologic resemblance to Fabry disease.[40,41] On histology, one sees enlarged podocytes with finely vacuolated cytoplasm. The vacuoles appear as clear spaces by LM because lipid is dissolved during tissue processing. Techniques used for electron microscopy (EM) sections preserve the lipid inclusions as methylene-blue granules; these are further resolved into curvilinear or whorled, lamellated "zebra" bodies ultrastructurally (Fig. 2). α-galactosidase A is the enzyme deficient in Fabry disease and chloroquine has the ability to inhibit the activity of this enzyme, resulting in the accumulation of neutral glycosphingolipids in the lysosomes of cells.[42,43] Our experience with a number of cases reveals that there are subtle ultrastructural differences between Fabry disease and phospholipidosis secondary to chloroquine consumption. Firstly, the classic lamellated podocyte inclusions are more numerous in Fabry disease. Secondly, small round homogeneously dense granular inclusions within endothelial, mesangial or tubular cell mitochondria suggest chloroquine effect. Cohen et al emphasised the presence of dense granules in capillary luminal histiocytes and curvilinear bodies in skeletal muscle as clues to the correct diagnosis of chloroquine toxicity.[40]

Immune Complex Glomerulonephritis

A common mechanism for glomerular injury involves immune complex deposition along the sub-epithelial aspect of the GBM, giving rise to membranous glomerulonephritis (MGN). There are numerous drugs and chemicals associated with MGN, best known among them being gold and penicillamine. Others include NSAIDS,[44] certain COX-2 inhibitors,[45] mercury,[46-48] captopril,[49,50] lithium[51] (also implicated in MCD[52]), formaldehyde,[53] trimethadione[54] (anti-convulsant), probenecid[55] and 2-Mercaptopropionyl glycine[56] (synthetic antioxidant used in the treatment of cystinuria, and rheumatic, skin and liver disorders). Drug-induced and idiopathic MGN have remarkably similar morphologic features. Gold administered parenterally is more likely to cause nephropathy than the oral route.[57] MGN is the most frequently reported abnormality.[58] With EM, inclusions of gold (clustered together as elongated strands) occasionally are evident in tubular epithelial cells (most common site as shown in Fig. 3), podocytes and mesenchymal cells. Persons with rheumatoid arthritis who have never received gold therapy do develop MGN, raising a controversy as to the pathogenic role of the drug; despite this fact, the temporal relationship between gold administration and onset of proteinuria, resolution of glomerular lesions with drug cessation, demonstration of gold particles in the kidney and animal models of gold-induced MGN all point to a causal relationship. Penicillamine[59,60] and the structurally related bucillamine[61] bring about asymptomatic proteinuria or the nephrotic syndrome in a greater number of patients than gold as they have a wider usage. Unlike gold however, penicillamine occasionally produces more severe glomerular damage in the form of crescents, leading to the syndrome of rapidly progressive glomerulonephritis.[62,63] We have seen such a case of pauci-immune crescentic glomerulonephritis with co-existing MGN in the same biopsy from an 80 year-old woman with a 3 year history of penicillamine treatment for scleroderma (Fig. 4). Interestingly, idiopathic MGN is associated with the same HLA haplotype as gold and penicillamine toxicity (HLA-DRw3 and HLA-B8).[62]

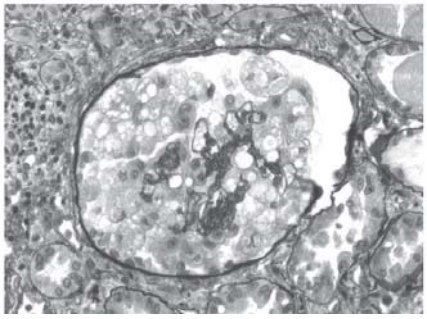

Fig. 1. Collapsing glomerulopathy: glomerular tuft is retracted, with overlying podocyte proliferation. The podocytes are enlarged, vacuolated and contain fuchsinophilic droplets. (Periodic acid-methenamine silver, original magnification x400).

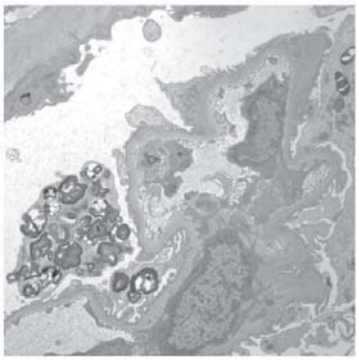

Fig. 2. Phospholipidosis: lipid inclusions in visceral epithelial cells. (Uranyl acetate and lead citrate, original magnification x7200).

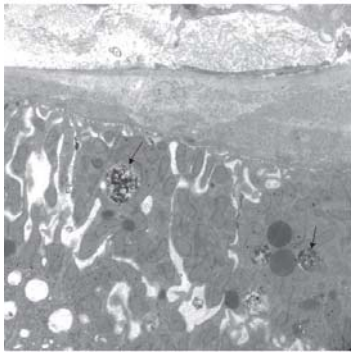

Fig. 3. Gold inclusions in membranous glomerulonephritis: aureosomes in proximal tubular cells. Similar inclusions are also present in podocytes and vascular smooth muscle cells. (Uranyl acetate and lead citrate, original magnification x10,000).

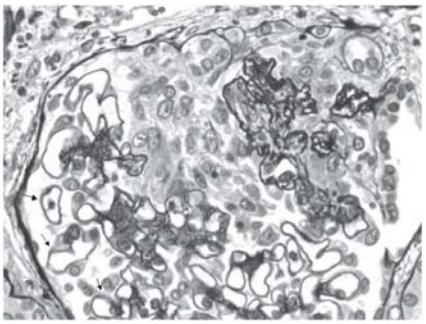

Fig. 4. Crescentic glomerulonephritis: the cellular crescent is clearly seen. There are subtle basement membrane vacuolations and small spikes. (Periodic acid-methenamine silver, original magnification x600).

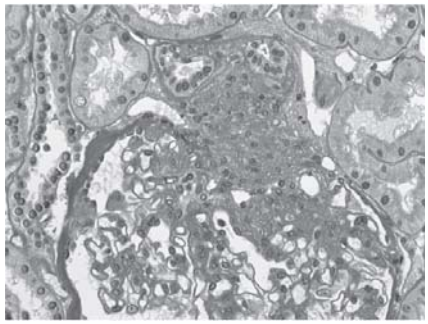

Fig. 5. CNI-associated lesion: JGA enlargement with accompanying segmental sclerosis. (Periodic acid-Schiff, original magnification x400).

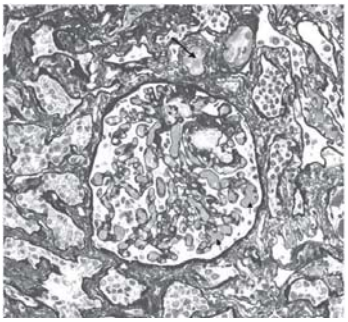

Fig. 6. Glomerular TMA: widespread intraglomerular thrombosis (small arrows). The afferent arteriole also has luminal fibrin thrombi (arrow). ATN is present in the same biopsy, not shown. (Periodic acid-methenamine silver, original magnification x400).

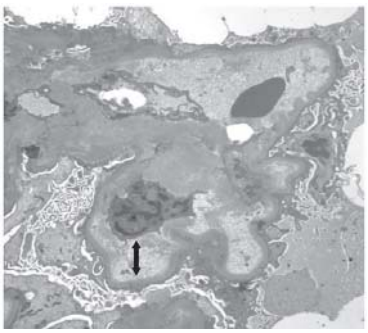

Fig. 7. Glomerular TMA: widened subendothelial lucent zone (double arrow head) containing flocculent material. (Uranyl acetate and lead citrate, original magnification x7200).

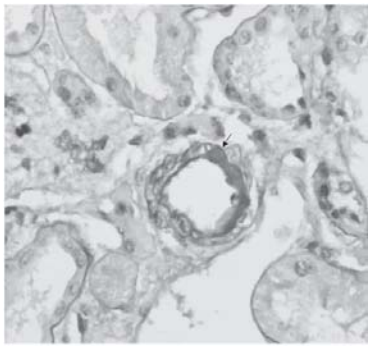

Fig. 8. CNI arteriolopathy: beaded arteriolar hyalinosis in an allograft biopsy. (Periodic acid-Schiff, original magnification x400).

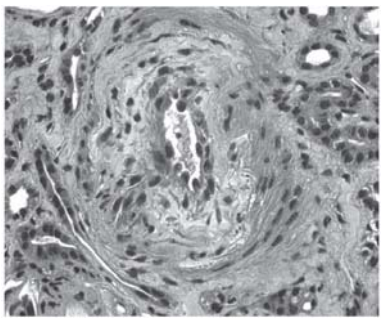

Fig. 9. Vascular TMA: the intima of this small artery is thickened by loose mucoid matrix, with significant luminal narrowing. (Haematoxylin and eosin, original magnification x600).

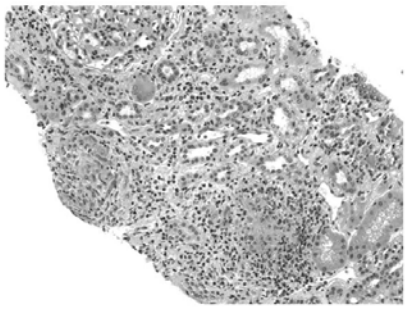

Fig. 10. Granulomatous interstitial nephritis: epithelioid granulomas and giant cells. (Haematoxylin and eosin, original magnification x200).

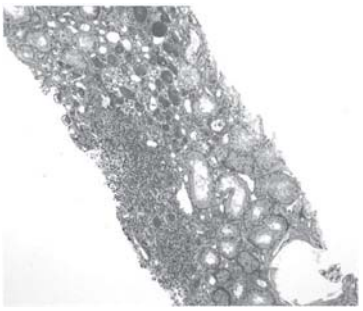

Fig. 11. Lithium toxicity: chronic inflammation with tubular atrophy and a microcyst (lower right corner) (Periodic acid-Schiff, original magnification x100).

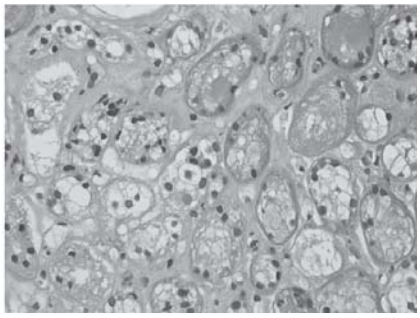

Fig. 12. Osmotic nephrosis: tubules undergoing necrosis but vacuoles are still visible, from an elderly person who presented with ARF following intravenous radiocontrast administration (Haematoxylin and eosin, original magnification x400).

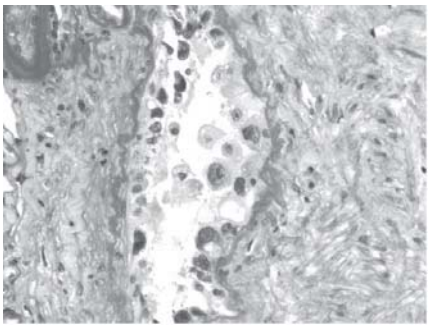

Fig. 13. Toxic effect of carboplatin: cell nuclei are enlarged, irregular and hyperchromatic (Periodic acid-Schiff, original magnification x600).

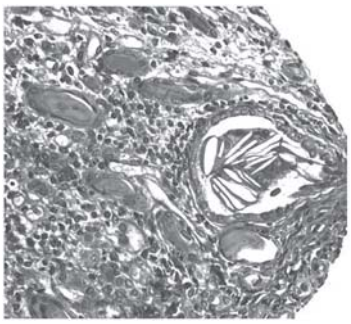

Fig. 14. Indinavir toxicity: crystals form clear spaces surrounded by giant cells in a dilated tubule. Features of chronic interstitial nephritis are present (Masson's trichrome, original magnification x200).

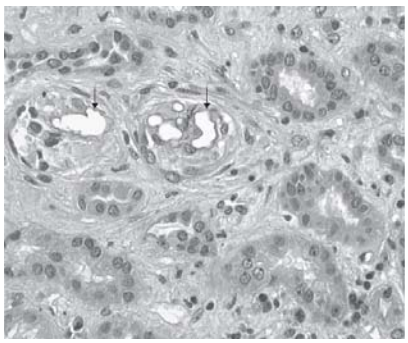

Fig. 15. Sodium phosphate nephrocalcinosis: interstitial deposition of round to irregularly-shaped calcifications. There is interstitial oedema with scattered lymphocytes (Haematoxylin and eosin, original magnification x200).

Investigations by Hess have estimated that drug-induced systemic lupus erythematosus (SLE) accounted for up to 10% of all SLE cases diagnosed in the United States.[64,65] In the long list of such medications, the common ones include procainamide, hydralazine, isoniazid, methyldopa, chlorpromazine, quinidine and propylthiouracil. Focal and diffuse proliferative patterns are frequent, and like primary lupus nephritis, mesangial and endocapillary hypercellularity with immune deposits characterise the glomerular changes. The distribution of deposits dictates the class of disease and they are usually so abundant (especially in class IV, *ISN/RPS classification of lupus nephritis 2004*) as to be easily recognised by LM. Suffice to say that subjects treated with drugs such as propylthiouracil and penicillamine may also develop focal segmental necrotising and crescentic forms of pauci-immune glomerular damage noted previously. To qualify as drug-induced lupus, a history of SLE must be absent prior to drug intake, and reversibility of clinical signs and serologic markers should also be documented. Anti-nuclear and anti-histone antibodies are often positive in these patients.

Pauci-immune Glomerulonephritis

Cases of pauci-immune crescentic glomerulonephritis in patients treated with infliximab (anti-TNF α monoclonal antibody) for rheumatoid arthritis have been reported.[66,67] Ashok et al described positive antineutrophil cytoplasmic antibody (C-ANCA) in their patient who was given infliximab.[67] Propylthiouracil and other anti-thyroid medications induce circulating MPO-ANCA,[68] adding to the expanding list of agents associated with pauci-immune crescentic glomerulonephritis with or without systemic small vessel vasculitis.[69,70]

Glomerular Endothelial Injury

Many drugs are known to cause thrombotic microangiopathy (TMA) and produce a clinical picture resembling haemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP). Cyclosporine, quinine, mitomycin C and other chemotherapeutic agents are best

examples. The renal toxicity of calcineurin inhibitors (CNIS) have been reviewed by Colvin and Nickeleit.[71] In this section, we shall concentrate on glomerular changes. Both cyclosporine A (the first CNI to be on the market) and tacrolimus have similar toxic side-effects and histologic lesions. At the functional level, CNIS interact with the renin-angiotensin system, causing vasoconstriction and hyperplasia/hypertrophy of the juxtaglomerular apparatus (JGA) in laboratory animals.[72-74] Their effects on the human JGA is less clear, although in our experience, JGA enlargement (Fig. 5) with an increased number of renin granules is not uncommon in renal allografts. Manifestations of the enlarged JGA are thickened afferent and efferent arterioles and prominent lacis cells. Ischaemia is perhaps contributory in this regard. With EM, endothelial cell swelling and detachment may be the earliest structural lesions. More severe TMA-type changes manifest as intracapillary thrombi with capillary wall remodelling or double contours and mesangiolysis; such glomerular lesions can occur in isolation or together with arteriolar thrombi (Fig. 6). Immunofluorescence studies often show fibrin or fibrinogen in the peripheral capillary walls and by EM, classic HUS/TTP alterations to the lamina rara interna are very common (Fig. 7). With chronicity, glomerulosclerosis supervenes.

Bevacizumab belongs to a class of chemotherapeutic agents that inhibits the function of vascular endothelial growth factor (VEGF). At the time of writing, only 2 reports have implicated it with TMA.[75,76] Patients may present with acute renal failure as a result of acute ischaemic-type tubular injury. VEGF is a growth factor for endothelial cells, necessary for glomerular endothelial cell growth and maintenance of fenestrae.[77,78] In extraglomerular vasculature, VEGF mediates endothelial cell differentiation/proliferation and vascular tone/permeability.[79] It is therefore conceivable that by targeting VEGF, bevacizumab could induce endothelial injury and TMA.

Vascular Injury

This section deals with the extraglomerular vasculature. CNIS typically affect the afferent arterioles and lesions can be seen from days to several weeks after the onset of treatment. The earliest abnormalities are swelling of medial smooth muscle cells and injury to endothelial cells and myocytes; nodular hyalinosis (classic calcineurin inhibitor arteriolopathy) develops subsequently.[80,81] These are mostly peripheral (medial or adventitial), replacing smooth muscle cells and contrasting with hypertensive arteriolar hyalinosis in that the latter has subintimal nodules usually co-existing with intimal fibroelastosis. It can be difficult to distinguish between hyalinosis due to cyclosporine (Fig. 8) and that resulting from diabetes mellitus as the two can look remarkably similar. Finding other tell-tale morphologic features of diabetic nephropathy (e.g. nodular glomerulosclerosis, glomerular insudates) and correlation with clinical history give the best chance of a correct interpretation. There are 2 scoring schemes for calcineurin inhibitor arteriolopathy – the Banff 1997 system[82] and the one developed by Mihatsch. The latter uses the number and extent of arteriolar involvement, producing 4 grades (ha0-3).[83] TMA is seen in more severe instances of CNI toxicity, with luminal fibrin thrombi, fibrinoid change in arteriolar wall and mucoid (hyaluronic acid-rich) intimal thickening (Fig. 9) developing earlier on, giving rise to concentric intimal fibrosis in the chronic stage. All these changes lead to vascular occlusion and parenchymal ischaemia. At times, regardless of aetiology, glomeruloid structures may develop consequent to arteriolar thrombosis followed by organisation. By IF, fibrin-related antigens are deposited in the walls of small arteries and arterioles. Ultrastructural examination[84] may disclose endothelial swelling and detachment; not unlike the glomerular capillary wall, there is subintimal widening by a lucent zone that often has electron-dense granules and strands. Fibrin tactoids, platelets and variably electron-dense material make up the thrombus. While still on the subject of transplant pathology, we must also mention that OKT3 (anti-CD3 monoclonal antibody)[85] and rapamycin (sirolimus)[86] are both associated with TMA; the latter in addition has been shown to cause proteinuria and tubular casts mimicking myeloma associated nephropathy. In general, the severity of vascular damage correlates well with renal prognosis.

Cocaine, both a stimulant and an appetite suppressant, is a thrombogenic substance that causes intense vasoconstriction potentially leading to TMA and acute renal failure (ARF).[87,88] The same substances that cause thrombosis in glomeruli (described above) obviously produce TMA in the vascular compartment, and will not be further elaborated. While strictly not a drug, octreotide (a low molecular weight carrier peptide) enhances the toxicity (TMA-type injury) of radionuclide therapy for cancers because it is readily filtered and taken up by the kidney. Inflammatory vasculitis secondary to the effects of drugs is generally uncommon, especially in the absence of ANCA.[89] Shih et al have reported necrotising vasculitis in the kidney of 2 patients treated with ciprofloxacin.[90] Granulomatous arteritis in patients taking phenytoin[91] and methicillin-induced vascular changes[92] are also on record.

Tubulointerstitial Injury

Immune-mediated Tubulointerstitial Inflammation

The most common cause of tubulointerstitial nephritis is drug related.[93] Antibiotics and analgesics (including NSAIDS) probably account for a significant proportion of these cases because they are widely available and used in large quantities throughout the world. Newer families of

drugs are continuously being recognised as contributing to acute interstitial nephritis, among them the proton-pump inhibitors (e.g. omeprazole). While antibiotics often produce a systemic hypersensitivity reaction (producing fever, skin rash, eosinophilia), NSAIDS trigger a cell-mediated or delayed-type hypersensitivity response. The third mechanism implicated is the formation of immune complexes. These may be pre-formed in the circulation. Otherwise, anti-tubular basement membrane (TBM) antibodies may direct themselves against TBM antigens, with the offending agent acting as hapten (as for methicillin). Considerable morphologic overlap exists between NSAID- and antibiotic-related interstitial nephritis. The acute stage is characterised by interstitial oedema and an infiltrate of predominantly mononuclear cells. Large numbers of neutrophils on the other hand suggest infection. When tubular atrophy/interstitial fibrosis sets in, the disease is deemed chronic. Sulfonamides sometimes predispose to crystal deposition (see below) and can result in urolithiasis and obstructive changes. Many drugs can induce a granulomatous reaction (Fig. 10) but granulomas are of course a hallmark of certain infections. They are also a feature of sarcoidosis, and are commonly found around necrotising glomerular lesions, crystals and foreign bodies. Tissue eosinophilia is most frequently seen with the antimicrobials (e.g. methicillin, sulfonamides, vancomycin). However staining protocols using alcoholic Bouin's fixative, a popular method for medical renal biopsies, often do not show degranulated eosinophils. Eosinophiluria as a screening test for allergic interstitial nephritis also has a low positive predictive value.[94] Ancillary IF and EM examination are of limited help but can help elucidate the pathogenic mechanism of injury. For example, linear deposits of antibody and complement along the TBM suggest antibody-mediated inflammatory response. Granular and corresponding electron-dense deposits in the TBM or interstitium implicate an immune complex mechanism. In chronic interstitial nephritis, the TBM is thickened and often lamellated when viewed under the electron microscope. Clinically, ARF with a mild degree of proteinuria characterises tubulointerstitial dysfunction. If the proximal tubules are the primary target, type II renal tubular acidosis (glycosuria, aminoaciduria, phosphaturia, uricosuria) manifests itself. Distal tubular damage (type I renal tubular acidosis) leads to imbalances in sodium and potassium salts. Involvement of collecting ducts in the medulla and papillae produces dilute urine and polyuria.

Analgesic Nephropathy and Chronic Forms of Injury

When combination analgesics are used in large cumulative doses, a more serious form of renal damage termed *analgesic nephropathy* may be seen. As phenacetin is no longer on the market, drug combinations usually refer to paracetamol and aspirin or other salicylates. Gross appearance and early light microscopic findings are most distinctive of this entity. The kidneys are small and shrunken, with irregular contours and papillary calcifications. On histology, the capillaries beneath the urothelium in the renal pelvis exhibit basement membrane thickening and calcification. This vascular injury leads to papillary ischaemia and eventual necrosis. Necrotic tissue may slough off or become calcified. There is compensatory hypertrophy of the columns of Bertin while the suprapapillary cortex undergoes atrophy. The link between phenacetin and urothelial carcinoma of the upper urinary tract had been established more than 2 decades ago.[95] This relationship is less conclusive with newer drug combinations. Moreover, results from the physicians' health study underscore the importance of co-existing risk factors (such as age, gender, hypertension and renal impairment) contributing to the pathogenesis of analgesic abuse.[96]

Lithium is prescribed for the treatment of bipolar disorders. Like the compound analgesics, an acute phase of renal injury is not usually encountered in a biopsy. Nephrogenic diabetes insipidus is the most common side effect,[97] possibly resulting from down regulation of aquaporin-2 expression in the collecting duct.[98] With long-term use, chronic tubulointerstitial nephritis and tubular microcysts are identified (Fig. 11), features which are not at all specific without the history. A form of chronic interstitial nephritis connected with an attendant increased risk of urothelial carcinoma, widely termed "Chinese Herb" nephropathy, was first described in Belgian women taking a herbal preparation for weight reduction.[99,100] The nephrotoxin has been identified as aristolochic acid from *Aristolochia fangchi*. Patients typically present with sub-acute renal failure, proteinuria and anaemia, progressing to ESRD over several months. Histology reveals a paucity of inflammation, given the extensive tubular atrophy/interstitial fibrosis and arterionephrosclerosis that are most remarkable in the outer cortex.[101] Clearly, many herbs do not contain aristolochic acid, yet cause renal impairment.

Toxic Tubulopathy

This paragraph summarises the cytopathic effects a number of drugs bring about on the renal tubules. Common to all, varying degrees of tubular degeneration and regeneration are observed. Luminal casts composed of sloughed epithelial cells, cell debris and proteinaceous material are a frequent finding. Some tubules become dilated and simplified, predisposing to rupture in more advanced cases. The plasma volume expanders (dextran, mannitol)[102,103] and sucrose-rich intravenous immune globulin (IVIG)[104] are known to induce *osmotic nephrosis*. In this condition, uptake of macromolecules into proximal tubular cells results in an increased osmotic gradient across

the plasma membrane; water is then drawn into the cells which become swollen and vacuolated, though generally still having intact brush borders. Such cellular vacuolation can be almost identical to the isometric vacuolation seen with CNI toxic tubulopathy and the effects of radiocontrast agents (fig. 12). Although rather similar in appearance by LM, different manifestations of injury may be appreciated at the sub-cellular level; for CNIS, investigators found dilated smooth endoplasmic reticulum and giant mitochondria by EM[105] while in the case of radiocontrast agents, the vacuoles represented invaginations of lateral tubular cell membranes.[106] Cisplatin and carboplatin belong to a class of chemotherapeutic drugs known as DNA alkylating agents that have a direct toxic effect on tubular cells, producing a tubulointerstitial pattern of injury. Nephrotoxicity is dose related. Carboplatin is thought to be less toxic than cisplatin. Hypomagnesemia[107] associated with the latter contributes to its toxic profile. Figure 13 demonstrates nuclear atypia in a proximal tubule from an elderly woman given carboplatin for breast carcinoma; neither significant inflammation nor ATN was present elsewhere. Narcotic substances cause rhabdomyolysis and ARF from time to time. Myoglobin casts may then be identified, precipitating in tubules and contributing to tubular obstruction and injury. These casts are easily overlooked as they are lightly pigmented. However, they stain red with trichrome and often appear tan-orangey with haematoxylin and eosin. When in doubt, an immunostain for myoglobin is helpful. The aminoglycoside antibiotics have long been shown to be nephrotoxic. Tubular injury seems the most likely explanation, and autophagic vacuoles (cyto-segresomes) containing myeloid bodies were observed in tubular epithelium from an early report of gentamicin therapy.[108] Lately, Markowitz et al noted the occurrence of ATN in 6 patients treated with the highly potent bisphosphonate zoledronate.[109]

Injury due to Crystallisation of Substances

There are chemical agents and medications that cause kidney damage by forming crystalline deposits, resulting in tubular injury, interstitial inflammation and obstruction. Most of the time, these drugs or their metabolites crystallise when they become supersaturated in the urine. Volume depletion (dehydration), conditions favouring nucleation and the lack of urinary inhibitors of stone formation are contributing factors. Hypercalcaemia due to excess vitamin D causes calcium phosphate to be deposited. Consuming large quantities of vitamin C[110] (metabolised to oxalic acid) or star fruit juice (contains oxalate) allows calcium oxalate crystals to form; unlike the phosphate salts, these are birefringent and are brightly decorated by polarised microscopy. Oxalate crystals are also seen with diethylene glycol poisoning, but it is useful to bear in mind that they can accumulate in any type of renal insufficiency (especially end-stage or transplanted kidneys). Many drugs induce hyperuricemia (common ones include alcohol, thiazide diuretics, cyclosporine, furosemide, cisplatin), and the chemotherapeutic agents may trigger a *tumor lysis syndrome*, causing uric acid nephropathy. The crystals are needle-shaped and negatively birefringent on frozen sections. They are mostly dissolved with routine tissue processing, forming amorphous aggregates surrounded by giant cells. Acute uric acid nephropathy is fortunately quite uncommon but it has a characteristic gross appearance. The kidneys display linear yellow striations in the medulla and papillae, corresponding to the distribution of the collecting ducts in which the crystals have precipitated.[111] Sulfadiazine,[112] indinavir[113,114] and acyclovir[115] have all been associated with tubular crystallopathy, urolithiasis and interstitial nephritis. The crystals, like those of uric acid, often dissolve and form empty acicular spaces engulfed by histiocytes (Fig. 14). Besides forming crystals, the highly active anti-retroviral agents such as tenofovir often bring about mitochondrial injury.[116] Acute nephrocalcinosis following the use of oral sodium phosphate solutions for colonoscopy result in calcium phosphate crystallisation. Before this link was established,[117,118] ARF that developed after consumption of this type of purgative was simply not appreciated. Elderly persons concurrently taking anti-hypertensive medications (diuretic, angiotensin converting enzyme inhibitor or angiotensin receptor blocker) or are dehydrated are most at risk. In a recent editorial in the Journal of the American Society of Nephrology, Markowitz and others compared the findings from 2 observational, retrospective studies looking at the association between oral sodium phosphate purgative use and kidney injury. They argued that renal damage remained an important issue, despite one of the studies claiming the opposite at 6 months follow-up.[119-121] The calcium phosphate crystals are non-polarisable and, unlike those that are commonplace in tissue dystrophic calcification, have a peculiar configuration. They are round to irregular, have a clear centre and refractile rim, at times with a bubbly appearance (Fig. 15).

In conclusion, while some drugs primarily injure a specific renal parenchymal structure, effects are seen in other compartments because they are inter-connected by feedback mechanisms. Physicians should be familiar with the wide range of medications harmful to the kidney, and be aware of the lesions they bring about. The incidence of drug-induced nephrotoxicity will only rise in tandem with the worldwide ageing population. This is due to frequent co-morbidities, polypharmacy and background age-related structural changes in the kidney.

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