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Tacrolimus (FK506)-Associated Renal Pathology

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Tacrolimus (FK506) is now an accepted primary immunosuppressive agent after solid-organ transplantation (1–13). It has both short-term and long-term advantages over conventional drugs: it is associated with less frequent rejection, hypertension, and hypercholesterolemia compared with cyclosporine. It also has been used to salvage allografts with acute cellular rejection not responding to cyclosporine and OKT3 (4–6,8,14,15).

Cyclosporine and tacrolimus are structurally unrelated compounds and bind to different cytosolic proteins in target cells. Nonetheless, both drugs have a closely related mechanism of action that is related primarily to a block in the transcription of interleukin-2 mRNA (16). This basic similarity in the mechanism of action is paralleled by an overlap in their toxicity profile: both drugs are toxic principally to the kidneys, central nervous system, gastrointestinal tract, and islets of Langerhans. The overall incidence of adverse events depends on dosage and clinical experience but appears to be comparable for both agents (7,11,17). Two multicenter trials report tacrolimus to have higher nephrotoxicity, neurotoxicity, and diabetogenicity (18, 19), but these conclusions have been criticized (20).

The following review focuses on the nephrotoxic actions of tacrolimus with particular reference to the associated histopathological changes seen in the allograft kidney. Throughout the discussion, emphasis is on how similar these changes are to those reported with cyclosporine therapy.

MECHANISMS OF TACROLIMUS NEPHROTOXICITY

The mechanism of immunosuppression mediated by cyclosporine and tacrolimus has been investigated intensively. It is believed that these drugs first must bind to their respective intracellular immunophilin receptors, particularly cyclophilin A and FK506 binding protein 12 (FKBP12). The immunophilin drug complex inactivates a phosphatase called calcineurin, which acts on additional target proteins that ultimately prevent the nuclear import of nuclear factor of activated T cells (NF-AT), a factor known to mediate the expression of several T-cell-activation genes. The resultant effects on the transcription and mRNA degradation of several cytokine genes have been described, of which the most important is interleukin-2, because this molecule plays a critical role in T-cell proliferation associated with alloimmune reactions (21).

The molecular basis of cyclosporine and tacrolimus nephrotoxicity is less well understood, but there is evidence that it may be mediated by the calcineurin pathway as well. Thus,

cyclosporine and tacrolimus binding proteins are present at a high concentration in the kidney (higher than in the liver and spleen). Calcineurin immunoreactivity and enzyme activity in the kidney can be specifically inhibited by tacrolimus or cyclosporine but not by rapamycin, a drug that blocks a different cell signal involved in the T-cell proliferative response to interleukin-2 (22, 23). At the cellular level, morphologic observations (reviewed subsequently) suggest that tubular epithelial cells, vascular endothelial cells, arteriolar myocytes, and interstitial fibroblasts are all targets for cyclosporine and tacrolimus nephrotoxicity.

The occurrence of epithelial vacuolization in clinical biopsy material suggests a direct toxic effect of tacrolimus and cyclosporine on the renal tubule. The exact mechanism of this toxicity, is not fully understood. Tacrolimus-induced inhibition of phosphoenol pyruvate Carboxylkinase is reported, but its physiological significance is uncertain. An antiproliferative action of tacrolimus on the renal tubular epithelium also has been described (24). For cyclosporine, it has been suggested that the drug accumulates in the lysosomes, disrupts lysosomal integrity, and releases intracellular toxins (25). Another theory holds that cyclosporine impairs tubular cell respiration by inhibiting oxidative phosphorylation, which results in depletion of adenosine triphosphate, accumulation of hypoxanthine, and generation of toxic oxygen free radicals (26,27). Whether any of these potential abnormalities are causally related to calcineurin inhibition is presently unknown.

Vasospasm leading to reduced glomerular filtration appears to be a key element in the vascular toxicity tacrolimus and cyclosporine (28). The principal associated morphologic finding is arteriolar myocyte vacuolization, which may reflect a direct toxic effect of the drug on smooth-muscle cells. (29). Data on cyclosporine-treated patients suggest that renin-producing cells may be particularly sensitive to this effect (30). Many biochemical correlates of, reduced renal blood flow and drug-induced hypertension have been described, but their relative contributions have not been defined. Reported observations, included increased thromboxanes, endothelin, or renin; enhanced sympathetic activity; decreased vasodilating prostanoids; and impaired nitric oxide production (31–33). Direct drug-induced injury to the endothelium, enhanced platelet aggregation by thromboxane A₂, and an impaired fibrinolytic pathway are potential explanations for the occasional development of micro-thrombi and hemolytic uremic syndrome following cyclosporine and tacrolimus therapy (33,34). The chronic vascular hyaline changes attributed to tacrolimus could, be, in part, the aftermath of acute endothelial injury, persistent, vasospasm, and hypertension. The renin-angiotensin system may also be involved because the drug Losartan (an angiotensin II receptor type I antagonist) reduces cyclosporine-induced arteriolar hyalinosis in rats, (35). A conceptual framework for the latter effect is provided by experiments showing that angiotensin II is a growth promoter for vascular smooth muscle (36).

Interstitial fibrosis is recognized as one of the lesions associated with chronic cyclosporine and tacrolimus nephrotoxicity, which, can be partly explained by drug-induced narrowing of small arteries and arterioles. As the narrowing proceeds, a linear zone of renal parenchyma situated in the watershed zone between adjacent vessels is deprived of its nutrition and, begins to undergo degenerative changes. There is also experimental evidence for a direct toxic effect of tacrolimus on the cortical medullary rays and medullary inner stripe. These areas of the renal parenchyma are particularly susceptible to injury because of their relatively low oxygen availability (37–39). This direct toxicity is morphologically characterized by tubular degeneration and atrophy, leading to fibrosis. The cytokine transforming growth factor beta (TGF- β), a well-known activator of collagen, transcription, is likely involved in the pathogenesis of interstitial fibrosis. Cyclosporine stimulates TGF- β in tubular epithelial as well as interstitial fibroblast cell line and stimulates mRNA expression of different collagens in renal tissue (40). Proliferation of tubular and interstitial

cells and an influx of macrophages precede the actual development of fibrosis in a salt-depleted model of chronic cyclosporine nephropathy (41). Work; with Losartan-treated animals suggests that the renin-angiotensin system participates in the development of interstitial fibrosis (42)

CLINICAL FEATURES OF TACROLIMUS NEPHROTOXICITY

Tacrolimus nephrotoxicity occurs in 17 to 44% of renal transplant recipients and in 18 to 42% of liver transplant recipients (18,43–45). Heart and lung, transplant recipients have not been systematically studied to define precisely the magnitude of nephrotoxicity in that in that patient population (46,47). The wide range in reported incidence depends not only on the dosing regimen but also on prior clinical experience with the drug (11,17). Thus, the Japanese multicenter study recorded a 44% incidence, of nephrotoxicity when tacrolimus was administered at a dose of 0.3, mg/kg/day. Subsequently, with additional experience and the use of tacrolimus at a lower dose, a reduction in incidence to 20.5% was observed (11). We found biopsy-proven acute reversible tacrolimus nephrotoxicity in 17% of renal-transplant recipients on an initial maintenance dose of 0.15 mg/kg of tacrolimus twice daily (48). These data pertain to the use of tacrolimus as a primary immunosuppressant after renal transplantation. In patients receiving intravenous tacrolimus as “rescue” therapy for refractory renal or hepatic allograft rejection, initial nephrotoxicity is seen in nearly all patients (8,49–51).

Clinically, acute tacrolimus nephrotoxicity can be defined as arise in blood urea or serum creatinine levels not explained by other factors, which may be prerenal (dehydration, heart failure, sepsis), renal (rejection, acute tubular necrosis, interstitial nephritis, tubulotoxic antibiotics, glomerulonephritis), or postrenal (ureteric obstruction, renal vascular thrombosis). It is important to stress that the diagnosis must be made by the process of exclusion. In allograft kidneys, it may be necessary to show on absence of acute rejection by biopsy, whereas in liver-transplant patients, hepatorenal syndrome and hepatic glomerulopathies are considerations in the differential diagnosis. Likewise, in heart and lung transplant recipients, atherosclerotic and hypertensive nephropathy need to be excluded before making a diagnosis of tacrolimus nephrotoxicity. The clinical diagnosis is most secure when there is a decrease in serum creatinine levels after a reduction in tacrolimus dosage; however, chronic tacrolimus nephrotoxicity may be nonreversible (11, 44) and, indeed, may not be detected unless routine monitoring of serum creatinine is supplemented periodically by creatinine clearance measurements. The distinction of chronic tacrolimus nephrotoxicity from insidiously developing chronic rejection is difficult on clinical grounds.

The temporal evolution of acute tacrolimus nephrotoxicity and its response to reduction in drug dosage have been described. The baseline creatinine level in one series of 22 patients was $212.2 \pm 168.0 \mu\text{mol/L}$ and showed a mean rise of $40.6\% \pm 14.2\%$ during episodes of nephrotoxicity (48). Concurrent extrarenal manifestations of tacrolimus toxicity were relatively common: hyperkalemia was recorded in 41% cases hyperglycemia in 36% of previously nondiabetic patients, and hand tremors (neurotoxicity) in 9% of subjects. The highest mean plasma and whole blood tacrolimus levels during the toxic episodes were $2.7 \pm 0.8 \text{ ng/ml}$ (normal range, 0.5–1.5) and $31.6 \pm 10.6 \text{ ng/ml}$ (normal range, 5–20), respectively. Nephrotoxicity episodes were associated with elevated plasma or whole blood in tacrolimus levels in 82% patients. In other studies, a correlation between blood tacrolimus levels and nephrotoxicity was observed by some authors (52–54) but not by others (45,55). The dose of tacrolimus was reduced stepwise in response to a diagnosis of tacrolimus nephrotoxicity until a satisfactory response in serum creatinine was obtained. The mean dose reduction was $41\% \pm 21\%$ (range, 11–89) and led to a $86\% \pm 18\%$ (range, 45–100) decrease in the serum creatinine level (48). This variation in the percent of dose reduction necessary to restore

allograft function reflects the known variability of tacrolimus pharmacokinetics in individual patients (56). The drug kinetics can be altered further by hepatic dysfunction and a variety of drug interactions. Thus, in patients receiving drugs that interfere with tacrolimus metabolism by the liver (itraconazole, erythromycin, diltiazem), drastic reductions in tacrolimus dosage may be required to reverse tacrolimus nephrotoxicity, and clinical response is delayed.

MORPHOLOGIC FINDINGS OF TACROLIMUS NEPHROTOXICITY

A description of the principal morphologic findings found in renal allograft biopsies performed during clinical episodes of tacrolimus nephrotoxicity follows.

Functional toxicity

Some patients on tacrolimus therapy develop laboratory evidence of graft dysfunction without remarkable morphological findings at biopsy. The renal dysfunction recovers as the dosage of tacrolimus is reduced. A similar phenomenon has been described with cyclosporine therapy and is believed to be the result of drug-induced vasospasm (57–58).

Acute tubular necrosis

Cyclosporine has been linked to the occurrence of acute tubular necrosis in the first several weeks after transplantation. Acute tubular necrosis during this interval can, of course, be due entirely to ischemic injury associated with the harvesting and implantation of the donor organ. There is experimental evidence, however, that immunosuppressive drugs can exaggerate such ischemic injury to the tubules (59). The frequency of acute renal failure and the duration of postoperative oliguria are greater in patients immunosuppressed with cyclosporine than with azathioprine (60). These observations also may be applicable to tacrolimus-treated patients, as this drug could potentiate renal ischemia by causing vasospasm, but clinical studies confirming this have not yet been performed.

Tubular vacuolization

Biopsies performed during clinical episodes of tacrolimus nephrotoxicity frequently show tubular vacuolization. In our experience, these tubular vacuoles are seen in proximal as well as distal tubules (Fig. 1). Although typically about equal in size and shape (isometric), focal coalescence into larger vacuoles is also demonstrable (61). The Japanese FK506 study group considers tacrolimus therapy to cause a “rough and foamy” tubular vacuolation in the proximal tubules (62). Cyclosporine toxicity is also associated with isometric tubular vacuolization, which is described by some authors to be found almost exclusively in the straight part of the proximal convoluted tubules (57). Tubular vacuolization may be better appreciated on trichrome compared with routine hematoxylin and eosin stains (63). Ultrastructurally, the vacuoles reflect dilatations in the endoplasmic reticulum (Fig. 2); some contain proteinaceous material and resemble lysosomes (61,63).

In addition to cyclosporine and tacrolimus toxicity, isometric tubular vacuolization has been described following administration of mannitol, dextran, sucrose solutions, and radiographic contrast media (57, 64). Such hyperosmolar tubular injury is the likely explanation for the tubular vacuolation observed occasionally in pretransplant donor biopsies. Isometric tubular vacuolization is said to be distinct from a coarser and more irregular vacuolation seen in ischemic injury. Some workers, however, report that the tubular vacuolization in patients clinically classified as cyclosporine toxicity is similar to that described in acute tubular necrosis (65). Likewise other studies show no differences in the spectrum of tubular changes in renal transplant patients treated with either cyclosporine or azathioprine (66,67). Experimental models of tacrolimus and cyclosporine toxicity with nonisometric tubular vacuolation also are described in the literature (68,69).

We commonly find isometric tubular vacuolization in biopsies with significant rejection and have wondered whether this might be the result of immunologically mediated injury in this setting. It is also possible to argue that these cases are examples of concurrent rejection and toxicity (25). From a practical standpoint, it is safe to use tubular vacuolization as flag indicating the need to lower the dose of tacrolimus or cyclosporine, provided the biopsy shows no change of rejection.

Myocyte vacuolization

Arteriolar myocyte vacuolization (Figs. 3 and 4) frequently accompanies tubular vacuolation in patients undergoing clinical episodes of tacrolimus and cyclosporine nephrotoxicity (61); however, this finding should be regarded as a nonspecific manifestation of vessel spasm (70) and attributed to immunosuppressive therapy only after exclusion of other causes of vascular injury. We have seen myocyte vacuolization in obvious rejection with florid intimal arteritis and in native kidneys with arteriolonephrosclerosis (unpublished observations). Amphotericin B can also cause striking smooth-muscle-cell vacuolization in the media of renal arterioles and small arteries (70). Analogous vacuolar change occurs in cardiac myocytes exposed to chemical, metabolic, and ischemic injury (71–74).

Tubular calcifications

Focal microcalcification in the renal parenchyma has been described in experimental tacrolimus and cyclosporine nephrotoxicity (75). Similar lesions occur in human biopsies (57,61) and, in some cases, may represent calcification of tubular epithelium damaged by these drugs; however, participants of one international workshop found the frequency of microcalcifications in patients on cyclosporine therapy to be comparable to that observed with azathioprine, a drug not considered nephrotoxic (66). The differential diagnosis includes dystrophic calcification at the site of prior ischemic or immunologic tubular injury and, less commonly, calcification resulting from hypercalcemic states, such as renal hyperparathyroidism.

Giant mitochondria

Giant mitochondria within the tubular epithelium have been demonstrated in tacrolimus-treated rats (59). We have not specifically looked for this lesion in human material, but literature is available on cyclosporine treated patients. Mihatsch et al. described round, oval, or cigar-shaped mitochondria up to half the size of the nucleus (57). These inclusions are rare even in cases with severe toxicity, and usually only one giant organelle is found per cell. Giant mitochondria and isometric vacuolation are said never to be observed in the same cell. Electron microscopy is needed for definite differentiation from phagolysosomes. The frequency of giant mitochondria in patients on cyclosporine therapy is higher compared with conventional immunosuppressive drugs in some series (57) but not in others (60). Giant mitochondria are not specific for cyclosporine toxicity and have been described in ischemia, glomerulonephritis, systemic lupus erythematosus, minimal change nephrotic syndrome, and patients receiving azathioprine.

Acute microvascular toxicity

Renal allografts maintained on cyclosporine show scattered thrombi in the glomerular capillaries and arterioles (fig. 5) in 3% of diagnostic biopsies (57). We found a comparable incidence of approximately 1% in our tacrolimus-treated patient (76). These observations may represent drug-induced injury to the endothelium or an effect on the coagulation pathway, perhaps involving the balance between thromboxane A₂ and prostaglandin PGI₂ (51). Clinically, patients may be asymptomatic, but when the changes are marked, hemolytic uremic syndrome (fig. 6) is reported (77–82). The thrombi may resolve completely or lead

to focal segmental thickening and duplication of the glomerular basement membranes. Electron microscopy shows a thickened lamina rara interna. Mesangial interposition is not seen, unlike transplant glomerulopathy. The differential diagnosis of thrombotic microangiopathy includes vascular rejection, acute cytomegalovirus infection, OKT3 therapy, malignant hypertension, disseminated intravascular coagulation and a recurrence of the original disease in patients transplanted for idiopathic hemolytic uremic syndrome or lupus erythematosus (57,76,83–86). A diagnosis of drug-induced microvascular toxicity should be made cautiously only after these conditions have been excluded. It appears that patients who develop cyclosporine-associated hemolytic uremic syndrome can be switched safely to tacrolimus (87–90). Reinstitution of cyclosporine also has been possible after clinical resolution, particularly if antiplatelet and renal vasodilator therapy is initiated (82,90). Conversely, tacrolimus-associated hemolytic uremic syndrome has been treated by switching the immunosuppression to cyclosporine (91). These observations suggest that the mechanisms of microvascular injury are not quite identical for these two drugs.

An acute arteriopathy involving small vessels less than two smooth-muscle cells thick has been linked to cyclosporine therapy (57,63). Onset is usually early after transplantation and is associated with high cyclosporine levels. The injury is possibly a manifestation of drug-induced vasospasm and is characterized by endothelial swelling, mucoid intimal thickening, and myocyte vacuolation. We reported four similar patients on tacrolimus therapy: One showed peculiar eosinophilic globules in the media, and another showed rare subendothelial lymphocytes and focal medial necrosis (76). Other similar cases have been reported from Japan and France (62,92). Differentiating these lesions from vascular rejection with intimal arteritis is both difficult and critical. The presence of significant lymphocytic infiltrates in the intima, scattered interstitial hemorrhages, tubulitis, and diffuse global glomerulitis favor the diagnosis of rejection over drug toxicity.

Before leaving this subject, it is of interest to recall that the potential of tacrolimus to cause injury to blood vessels was much debated during the developmental phase of this drug. Vascular damage described as “vasculitis” involving medium-sized arteries in the liver, pancreas, and heart was reported in tacrolimus-treated dogs (93). Work done by our colleagues and others raised doubts about the significance of these findings, as vasculitis was found with equal frequency in control animals (94,95). Studies in rats, baboons, and monkeys treated with tacrolimus (59,96) also were unable to reproduce vasculitis lesions. Arteriolar-sized renal vessels in rats and dogs treated with tacrolimus develop focal medial necrosis, accumulation of eosinophilic inclusions, and juxtaglomerular transformation but not true arteritis (94,97,98). In our opinion, these arteriolar lesions are similar to those reported with dopaminergic and adrenergic drugs and are adequately explained by intense vasospasm (99,100).

Arteriolar hyalinosis

Both cyclosporine and tacrolimus therapy are associated with hyaline eosinophilic deposits (Figs. 3 and 7) within the arterioles (57,61,101). Immunofluorescence examination shows these deposits to contain several proteins including fibrin, immunoglobulin M, C3, and C1q. Hyalinosis is particularly seen in patients on prolonged drug therapy, but this change conceivably can develop rapidly after acute arteriopathy. It is important to keep in mind that similar vascular changes can be seen as a result of aging, hypertension, and diabetes mellitus, which would explain why in some studies wherein cyclosporine is used at low dosage or the follow-up is relatively short, the incidence of hyalinosis is not significantly higher than in control biopsies (102,103). A nodular configuration to the hyalin has been considered characteristic of drug toxicity (57), but this feature has also been described in donor-transmitted nephrosclerosis and in patients dying of ischemic cardiomyopathy (104,105). Even after review of clinical data and previous biopsies, it is not always possible

to ascertain definitively the underlying cause of hyalinosis in individual biopsies, and sometimes multiple factors appear to be involved. Some authors find electron microscopy (Fig. 8) useful in this setting and state that in cyclosporine toxicity the hyaline deposits are circular and replace underlying necrotic smooth muscles, whereas in diabetes or hypertension, the deposits are not accompanied by degenerative or necrotizing changes in the myocytes (57). Other authors have been unable to find myocyte necrosis in cyclosporine-associated arteriolar hyalinosis, however, possibly because they looked at biopsies at a later stage of the disease (102,106). Detailed ultrastructural evaluations of tacrolimus-associated hyalin change are not reported in the literature.

Striped fibrosis

Prolonged use of cyclosporine and tacrolimus can cause interstitial fibrosis, which is said to have a “striped” pattern (57,61) resulting from areas of ischemic tubular atrophy and interstitial fibrosis alternating with relatively well-preserved or even hypertrophic renal tubules (Fig. 9). As already discussed, the underlying cause is, at least in part, a drug-induced thickening and hyalinization of interlobular arteries. In individual biopsies showing striped fibrosis, actual lesions of arteriolar narrowing are not always demonstrable, which could be merely a sampling problem or the result of a direct toxic effect of tacrolimus on the cortical medullary rays and medullary inner stripe (37,39).

Claims that striped fibrosis is specific for chronic drug toxicity are unfounded (107). Before attributing a striped pattern of fibrosis in allograft biopsies to drug-induced injury, other causes of interstitial fibrosis, such as glomerulonephritis, pyelonephritis, and renal artery stenosis, should be excluded. Mild striped fibrosis has also been described in donor transmitted nephrosclerosis (104). When striped fibrosis in a biopsy is associated with lesions of chronic vascular rejection, it may be difficult to determine the extent to which the fibrosis is really drug induced, indeed, it is likely that both chronic rejection and drug toxicity contribute to the evolution of fibrosis in most long-term renal allografts. Although striped fibrosis is presumably irreversible, a reduction in drug dosage nevertheless may improve renal function if there is coexistent functional toxicity due to vasospasm.

Diffuse interstitial fibrosis

If tacrolimus and cyclosporine can be accepted as causes of focal striped fibrosis, one can visualize how continued drug-induced injury might give rise to a more diffuse pattern of fibrosis; however, some authors have described diffuse interstitial fibrosis occurring within the first few weeks of transplantation and attributed it to tacrolimus or cyclosporine injury (62, 108). We have not seen this and believe that most such cases can be explained by preexisting donor disease or by healing of moderate to severe immunologic or ischemic injury.

Glomerular pathology

The occurrence of glomerular capillary and afferent arteriolar thrombosis as a manifestation of cyclosporine and tacrolimus nephrotoxicity has been mentioned earlier (76–82). In cases with frank hemolytic uremic syndrome, clinical resolution can be complete, but residual injury in the form of glomerular capillary basement membrane thickening and duplication may persist (109).

Experimental studies show that tacrolimus and cyclosporine can cause juxtaglomerular hyperplasia, possibly by a local activation of the renin-angiotensin system (37, 98). The diagnostic utility of this finding in clinical practice is limited because a study of the juxtaglomerular apparatus requires specialized histochemical techniques. Furthermore,

juxtaglomerular apparatus hyperplasia is a nonspecific finding described in other clinical settings, such as rejection, arteriosclerosis, hypertension, and reflux nephropathy (110).

The occurrence of focal segmental or global sclerosis is mentioned in the literature as one of the manifestations of chronic drug toxicity (102,111–113). It should be kept in mind, however, that focal segmental sclerosis is also a nonspecific lesion that may be observed in many diseases, including chronic rejection, renal artery stenosis, recurrent glomerulonephritis, and reflux nephropathy. The pathogenesis in cases of drug-induced injury may reflect segmental ischemic collapse of the glomerular capillary loops secondary to the lesion of arteriolar hyalinosis (57,61,101). Resolution of intraglomerular capillary thrombosis could account for some cases (76,82). Alternatively, the lesion could reflect a compensatory response to nephron loss caused by the vascular and interstitial effects of cyclosporine and tacrolimus. Thus, it is believed that compensatory glomerular hypertrophy can result in capillary hyperfiltration, endothelial injury, mesangial dysfunction, and progressive segmental or global glomerulosclerosis (114). A possible link between glomerulosclerosis and local activation of the renin angiotensin system is suggested by experiments demonstrating stimulation of extracellular matrix protein synthesis by rat glomerular mesangial cells exposed to angiotensin II (115). Mesangial matrix protein synthesis also can be enhanced by TGF- β , a cytokine known to be stimulated by cyclosporine (40).

NATURAL HISTORY OF TACROLIMUS NEPHROTOXICITY

Tacrolimus-induced tubular vacuolization, acute arteriolopathy, and thrombotic microangiopathy generally respond well to reduction in the drug dose; histologic improvement can be documented in follow-up biopsies. Studies specifically addressing the question of whether chronic tacrolimus nephrotoxicity results in progressive graft loss have not yet been published; however, data are available showing that long-term graft survival in tacrolimus-treated patients is superior to that reported for cyclosporine and azathioprine (a drug not considered nephrotoxic) (10). Hence, it is unlikely that chronic administration of tacrolimus is a frequent cause of graft loss.

The natural history of tacrolimus-associated arteriolar hyalinosis and interstitial fibrosis needs to be defined by examination of sequential biopsies from renal transplant recipients. Uncontrolled studies on cyclosporine-treated patients suggest that discontinuation of the drug leads to resolution of mild arteriolar hyalin deposits in some cases but to continued accumulation in other patients (116,117). In evaluating such data, it should be kept in mind that arteriolar hyalin deposits can be extremely focal in distribution and may involve fewer than 10% of vessels sampled at biopsy (116), leading to difficulty in distinguishing between sampling artefact and true resolution/progression of lesions in sequential biopsies (106). We have noted that striped fibrosis has a similar uneven distribution in renal allografts (61).

SUMMARY

A variety of renal lesions have been described in patients undergoing episodes of tacrolimus nephrotoxicity. Although helpful to the pathologist seeking morphologic clues to substantiate drug toxicity, none of these lesions is specific to the extent that it has not been reported in other conditions. This is not surprising because all organs in the human body possess only a limited repertoire of tissue reactions to deal with injurious stimuli. The diagnosis of tacrolimus nephrotoxicity is therefore best made with reference to the clinical context and after exclusion of other causes of graft dysfunction. The ultimate confirmation is a decline in serum creatinine levels following a reduction in tacrolimus dosage. Chronic tacrolimus nephrotoxicity can be nonreversible, however, and may be regarded as the “price to be paid” for maintaining continuous immunosuppression. Because the nephrotoxic and

antirejection actions of tacrolimus might be mechanistically related, it may not be possible to avoid tacrolimus nephrotoxicity altogether. Fortunately, there is evidence that the effects can be minimized by the use of low-dose regimens. Observed and projected long-term graft survivals with tacrolimus now equal or exceed those obtainable with alternative immunosuppressive drugs (10).

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FIG. 1.

Tubular vacuolization in patient with tacrolimus nephrotoxicity. The vacuoles vary somewhat in size and affect proximal as well as distal tubules.

FIG. 2.

Electron micrograph prepared from a biopsy with tacrolimus-associated tubular vacuolization. Most vacuoles appear to represent dilatations in the endoplasmic reticulum, but some have a morphology consistent with lysosomes.

FIG. 3.

This afferent arteriole from a patient with clinical tacrolimus nephrotoxicity shows myocyte vacuolization. Hyaline material can be seen deposited in the intima (periodic acid Schiff's stain).

FIG. 4.

Ultrastructurally, myocyte vacuoles resemble tubular vacuoles in that they reflect a combination of dilated endoplasmic reticulum and lysosomes.

FIG. 5.
Afferent arteriolar thrombosis in a renal transplant recipient biopsied for rising serum creatinine levels. The glomerular capillary loops show ischemic wrinkling.

FIG. 6.

Widespread glomerular capillary thrombosis in a patient with tacrolimus-associated hemolytic uremic syndrome. The detailed clinical course of this patient has been published (78).

FIG. 7. Periodic acid Schiff (PAS)-stained section illustrating arteriolar hyaline change associated with tacrolimus therapy. The smaller of the two arterioles in this photomicrograph shows early hyalinosis confined to the intima. The larger arteriole shows transmurular involvement, affecting greater than half its circumference, with hyalin material also lying in the vascular lumen.

FIG. 8.

Electron micrograph of an arteriole with severe tacrolimus-associated hyalinosis. There is massive accumulation of a highly electron-dense material, which takes circular to oval nodular profiles. The remnant myocytes show vacuolar degeneration.

FIG. 9.

A striped pattern of fibrosis seen in biopsy material from a patient on long-term tacrolimus therapy. This appearance is produced by areas of patchy fibrosis and tubular atrophy alternating with relatively normal parenchyma. It should be stressed that striped fibrosis is not a specific lesion and can be seen in many chronic disease, such as glomerulonephritis, pyelonephritis, renal artery stenosis, donor-transmitted nephrosclerosis and chronic vascular rejection.