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The Histopathological Changes Associated with Allograft Rejection and Drug Toxicity in Renal Transplant Recipients Maintained on FK506

Clinical Significance and Comparison with Cyclosporine

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The histopathological changes in 51 renal allograft biopsies from patients immunosuppressed with FK506 were compared with those seen in 30 needle biopsies obtained from patients on cyclosporine. The frequency and severity of rejection episodes were similar in both groups. Tubular vacuolation and myocyte vacuolation were found to be useful morphological markers to monitor short-term drug toxicity associated with both drugs. Long-term administration of FK506 led to striped interstitial fibrosis and arteriolar hyalinosis, similar to that previously documented for cyclosporine. One case each of hemolytic uremic syndrome and necrotizing arteriopathy was noted in patients receiving FK506. FK506 and cyclosporine are structurally unrelated compounds; hence the parallelism observed in their nephrotoxicity profile suggests that the interactions of these drugs with renal tissue involves the operation of two different initial signal-transducing mechanisms, ultimately activating the same final metabolic pathways.

Key Words: Renal—Kidney—Transplant—Drug—Toxicity—FK506—Cyclosporine.

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FK506 is a macrolide antibiotic estimated to be two to three orders of magnitude more potent as an immunosuppressant than cyclosporine (28,35). When used as the primary immunosuppressive agent in renal transplantation, it lowers or eliminates the need for concurrent steroid administration (19,30). It has also been used to salvage allografts with acute cellular rejection refractory to cyclosporine, even when OKT3 has been ineffective (9). An additional benefit is the lower incidence of hypertension, hypercholesterolemia, and hyperuricemia seen in the long-term follow-up of these cases (33). The University of Pittsburgh has conducted a prospective randomized trial to compare the efficacy of FK506 and cyclosporine in renal transplantation. The purpose of this report is to describe the patterns of rejection and drug toxicity observed in allograft needle biopsies obtained from these cases. Because FK506 will be increasingly used in renal transplantation, it is worthwhile for surgical pathologists to become familiar with these changes.

MATERIALS AND METHODS

Thirty-six patients undergoing renal transplantation at the Presbyterian University Hospital between February 1990 and May 1991 were randomly assigned to receive either FK506 or cyclosporine as the primary immunosuppressant. Details of the drug administration and therapeutic monitoring protocols used in these patients have been published

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TABLE 1. *Demographic characteristics of patients studied*

	FK506	Cyclosporine
Number	20	16
Median age (range)	35 yr (19–58)	38 yr (23–57)
Sex	9M, 11F	11M, 5F
Native renal disease	CG2, HT 5, DM 6, PK 2, HPL 1, SLE 3, UN 1	CG 7, HT 2, DM 3 PK 1, UN 3
Median biopsy follow-up (range)	91 days (7–531)	31 days (7–140)

CG, chronic glomerulonephritis; HT, hypertension; DM, diabetes mellitus; HPL, hypoplasia; SLE, systemic lupus erythematosus; UN, unknown; PK, polycystic kidney.

(28,30). The demographic characteristics of the cases studied are presented in Table 1.

Renal biopsies were performed in these cases as clinically indicated. These were routinely processed for paraffin embedding and sectioning at 2 μ. Two haematoxylin eosin stain, one periodic schiff stain, one Jones and one trichrome stain were done on each biopsy. The presence or absence of the following histopathological features was evaluated in each biopsy by two of the authors (P.S.R., A.J.D.) without knowledge of the immunosuppressive agents used in each case: glomerular cellularity, changes in glomerular mesangial matrix and capillary basement membranes, tubular and myocyte vacuolation, tubular necrosis, calcifications, lymphocytic infiltrates, edema, hemorrhage, fibrosis, endothelialitis, vessel hyalinoisis, thrombosis, necrotizing arteritis, arteriosclerosis, and arteriolosclerosis. The frequency of these changes in the FK506 and cyclosporine groups was compared.

The diagnosis of acute cellular rejection and a grading of its severity was done as follows: (a) minimal rejection was defined as sparse lymphoplasmacytic infiltrates, tubular damage, and venous lymphocytic infiltration that was not readily demonstrable; (b) mild rejection was defined as multiple discrete foci of activated lymphoplasmacytic infiltrates with tubulitis and venous endothelialitis; (c) moderate rejection was defined as confluence of foci of rejection used to define the mild grade; and (d) severe rejection was defined as tubular necrosis, tubular loss, and interstitial hemorrhage superimposed on a diffuse infiltrate of activated lymphocytes.

An impression of drug toxicity was conveyed to the clinicians when (a) tubular or myocyte vacuolation were prominent in the absence of overt features of acute rejection; (b) tubulointerstitial calcification was seen in the absence of recent acute tubular necrosis or end stage renal disease; (c) striped fibrosis was present without any other apparent cause for interstitial collagen deposition; or (d) vessel hyalinosis was documented in the absence of diabetes mellitus, donor disease, or significant clinical hypertension. Statistical comparisons were done using the chi-square test with Yates correction or Wilcoxon's Rank Sum Test.

RESULTS

The presence of interstitial infiltrates of activated lymphocytes, renal tubular damage, and venous endothelialitis were found to be reliable criteria for monitoring acute cellular rejection in FK506-treated allografts, as is already well established for patients receiving cyclosporine and other immunosuppressive agents. Likewise, conventional criteria, that is, extension of the lymphocytic infiltrate into arterial walls and the presence of glomerular neutrophilic infiltrates, platelet aggregation, and thrombosis, established the diagnosis of acute vascular rejection. The distribution of different grades of acute cellular rejection showed no striking differences between the FK506- and cyclosporine-treated groups; however, this grading system was useful to convey to the clinicians the urgency with which a given episode of rejection needed to be treated. For minimal acute cellular rejection, as defined here, patients could be simply kept under clinical surveillance; on the other hand, with moderate to severe rejection, significant augmentation of the level of immunosuppression was indicated.

The percentage of patients experiencing one or more episodes of acute cellular allograft rejection was higher in the cyclosporine group versus the FK506 group (88% vs. 55%, Table 2) despite the shorter median follow-up (Table 1) in the former group. A comparative study of the evolution of chronic vascular rejection and concomitant trans-

TABLE 2. *Allograft rejection in study population*[a]

	FK506	Cyclosporine
Patients enrolled	20	16
No. of biopsies	51	30
Incidence of rejection	55%	88%
Median onset post-transplant (days)	14 (range, 3–19)	20 (range, 4–135)
Severity of cellular rejection		
Minimal	28%	22%
Mild	36%	55%
Moderate	36%	23%

[a] No statistically significant differences were found between the FK506- and cyclosporine-treated groups.

plant glomerulopathy in this cohort of patients will require longer follow-up. At the time of this analysis, only two FK506-treated patients had developed significant light microscopic changes of this kind, at intervals of 151 and 385 days post-transplant.

The median times of onset for the first episode of drug toxicity were, respectively, 65 and 19 days post-transplant in the FK506 and cyclosporine treatment groups. An average of 1.4 episodes of drug toxicity was recorded in each FK506-treated patient, compared with 1.9 episode per cyclosporine-treated patient. Tubular or myocyte vacuolation was a particularly useful index of such episodes of drug toxicity (Figs. 1 and 2). Usually, vacuolation of both proximal and distal tubules could be demonstrated. The vacuoles were typically small and isometric with diameters not exceeding 20% of the nuclear diameter. However, focal confluence of these smaller vacuoles into larger ones was also present in a few microscopic fields. The morphology of the vacuoles did not differ in the cyclosporine- and FK506-treated patients. Vacuolation was present concomitantly with acute cellular rejection in 22 of 28 (79%) and in 14 of 22 (64%) of biopsies in the FK506 and cyclosporine groups, respectively (Table 3). Small focal calcifications involving scattered tubular epithelial cells, tubular basement membranes, or interstitium were seen in 40% of episodes of FK506 toxicity and in 15% of episodes of cyclosporine toxicity. Striped interstitial fibrosis was present in 35% and 23% of these two groups, respectively (Fig. 3). Vessel hyalinosis was found in 40% of FK506-treated patients versus 23% of cyclosporine-treated patients (Fig. 4). Lesions of focal glomerular sclerosis were found in two biopsies showing other changes compatible with FK506 toxicity.

One case had an arteriopathy involving the interlobular arteries characterized by deposition of a fibrinoid material in the intima, accompanied by endothelial prominence, mild intramural lymphocytic infiltrates, nuclear pyknosis and fragmentation (Fig. 5). This patient was a 19-year-old woman who received a kidney transplant for endstage renal disease of undetermined etiology. The biopsy showing the arteriopathy was obtained 24 days post-transplant because of rising blood urea and creatinine. The patient responded to a reduction in the dosage of FK506 and was discharged from the hospital. A follow-up biopsy 45 days later showed mild acute cellular rejection without any residual vascular lesions.

Finally, one case of thrombotic microangiopathy was observed in a patient on FK506 therapy (Fig. 6). This case, reported previously (27), was a 36-year-old woman transplanted for lupus nephritis. A hemolytic syndrome developed in the 9th month post-transplant. There was no history of any preceding upper respiratory viral respiratory infection or diarrhea, nor was any laboratory evidence of recurrent lupus found. FK506 was discontinued on the presumption of drug toxicity and replaced by azathioprine. The renal function improved over the course of 6 weeks and returned to baseline. Follow-up renal biopsies were not available.

DISCUSSION

FK506 and cyclosporine are structurally unrelated but mechanistically very similar immunosuppressive drugs that inhibit T-cell activation (10–12). The target receptors for these two drugs, FK binding protein and cyclophilin respectively, both possess peptidyl-prolyl *cis*-trans isomerase (PPI-ase) activity (6,34). Transcriptional regulation of inter-

TABLE 3. *Morphologic criteria of drug toxicity in allograft kidney biopsies*[a]

	FK506	Cyclosporine	Differential diagnosis
Acute drug toxicity			
Tubular vacuolation	17/20 (85%)	12/13 (92%)	Ischemia, mannitol
Myocyte vacuolation	16/20 (80%)	7/13 (54%)	Chemotherapy
Necrotizing arteritis	1/20 (5%)	0/13 (0%)	Vascular rejection
Thrombotic microangiopathy	1/20 (5%)	0/13 (0%)	Hemolytic uremic syndrome
Chronic drug toxicity			
Striped fibrosis	7/20 (35%)	3/13 (23%)	Chronic rejection, hypertension, renal artery stenosis
Peritubular calcifications	8/20 (40%)	2/13 (15%)	Acute tubular necrosis
Arteriolar hyalinosis	8/20 (40%)	3/13 (23%)	Diabetes, hypertension
Focal glomerulosclerosis (?)	2/20 (10%)	0/13 (0%)	Chronic rejection, recurrent or de novo glomerulonephritis

[a] The frequency of various morphologic findings in FK506-treated patients did not show any statistically significant differences compared with the cyclosporine-treated group.

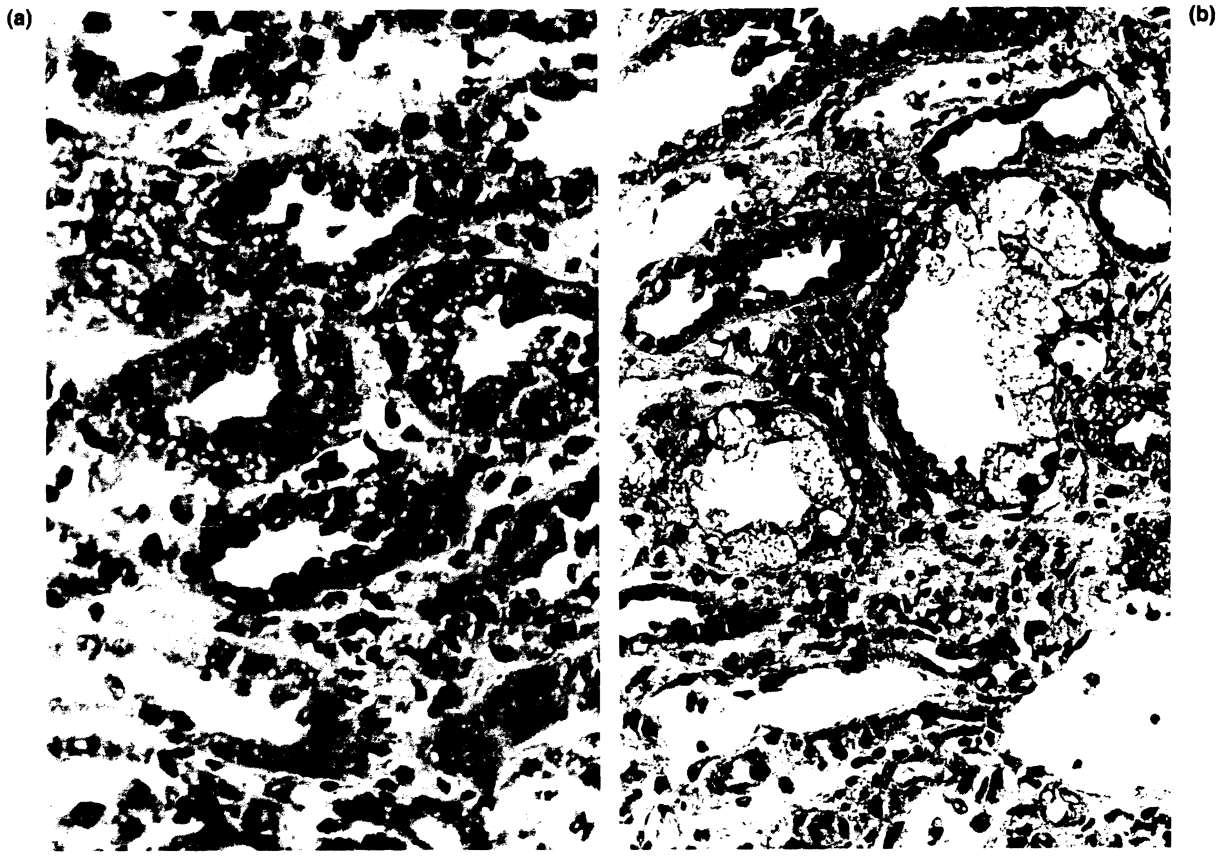

FIG. 1a,b. (a) The proximal and distal tubules in this patient with clinical FK506 toxicity show a fine cytoplasmic vacuolation. **(b)** In contrast, the vacuolation associated with ischemic injury, for example, acute tubular necrosis, is coarse and irregular. (Parts **c** and **d** shown on p. 64.)

leukin 2, interleukin 4, and gamma interferon seems to be the ultimate molecular basis for the inhibition of T-cell-dependent immune interactions observed with these drugs (10,38). A preliminary study from Pittsburgh found the spectrum of renal allograft pathology seen in patients treated with these two drugs to be quite similar (3,4).

The morphological features of drug toxicity in renal allograft biopsies were somewhat more frequent in the cyclosporine-treated patients (1.9 episodes per patient) than in patients on FK506 (1.4 episodes per patient). Varying degrees of tubular vacuolation was frequently demonstrable even in biopsies showing acute cellular rejection. If significant lymphocytic infiltration and tubular injury are present, it can be useful to treat for rejection despite the tubular vacuolation. Persistent tubular vacuolation after the rejection has resolved is then managed by a reduction in the dosage of FK506 or cyclosporine. Other possible causes of isometric tubular vacuolation, such as mannitol or dextran infusions and exposure to radiocontrast media, should be kept in mind (5,24). Myocyte vacuolation, when present, was accompanied by tubular vacuolation. A thickened medial layer in these vessels suggested an underlying element of vasospasm. The changes were generally reversible, regressing over several days as the drug dosage was reduced. This is in contrast to the smooth-muscle vacuolation seen in patients on chemotherapy, which may persist for several months after cessation of drug therapy.

Although the development of peritubular calcifications was typically a delayed phenomenon, sequential allograft biopsies occasionally showed that such calcifications could appear and then dissolve over several days. It seems that a fairly high turnover of calcium can occur in the renal parenchyma. These calcifications are probably dystrophic in nature and occur at sites of previous individual tubular cell necrosis mediated by drugs. There is evidence that ischemia exacerbates drug-induced tubular injury (26,27). Calcifications following pure ischemic injury to the tubules are larger and coarser compared with those seen in drug toxicity.

Striped fibrosis (14,36) is a picturesque term applied to parallel bands of cortical interstitial fibrosis running perpendicular to the renal capsule and separated by foci of atrophic tubules. The distribution

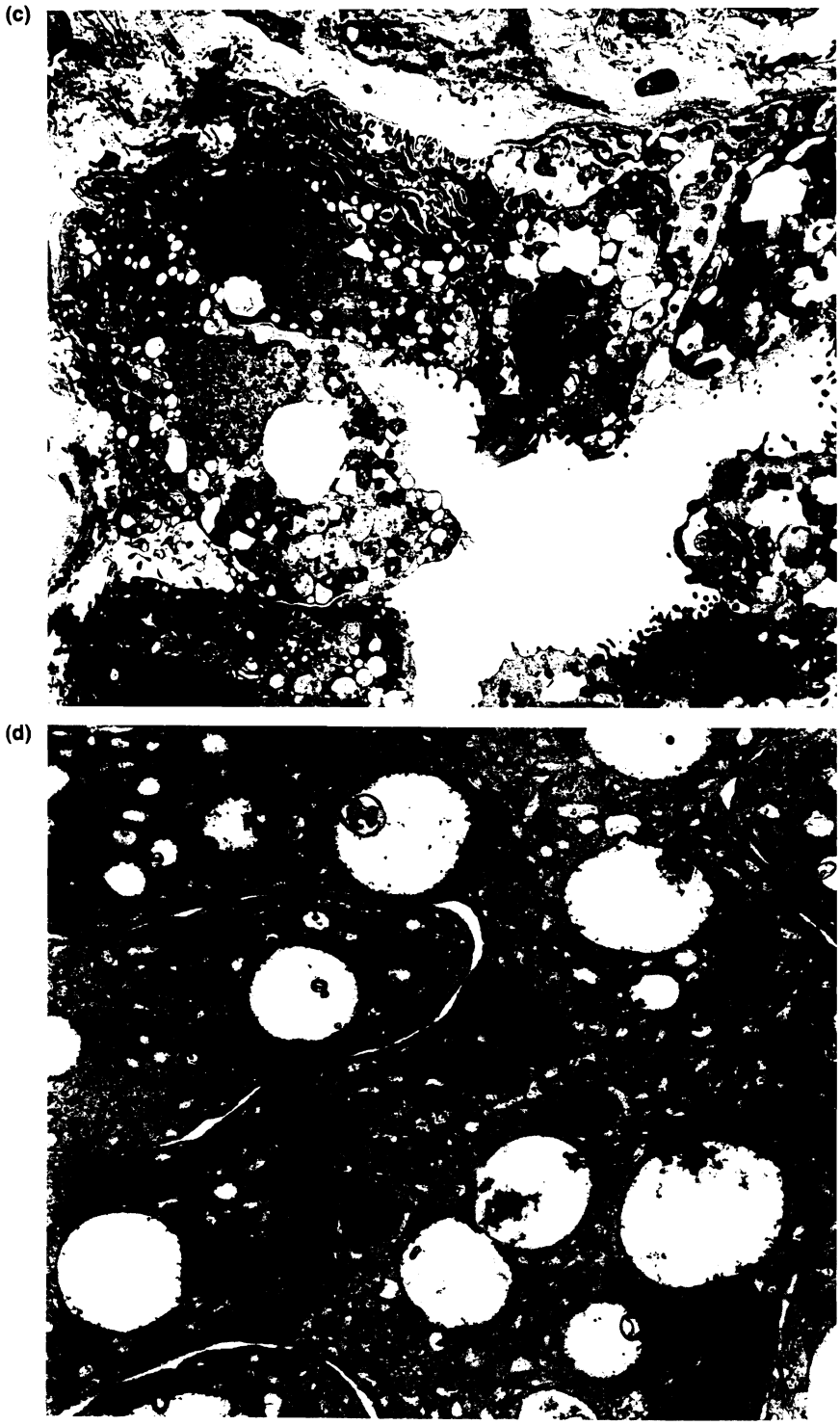

FIG. 1c,d. (c) Panoramic electron micrographic view of FK506-induced tubular vacuolization (×3000). **(d)** At higher magnification, the vacuoles represent dilatations of the endoplasmic reticulum and lysosomal elements (×13,000).

of the fibrosis suggests that the underlying pathogenetic mechanism is an ischemic tubular atrophy and fibrous replacement in the watershed zones of renal parenchyma lying between adjacent cortical arteries. In the literature on cyclosporine, striped fibrosis has implied chronic drug toxicity (22); however, it is merely the end result of a vaso-occlusive process, so that hypertension, transplant vasculopathy, and renal artery stenosis should be excluded before accepting these lesions as evidence of a chronic toxic insult to the kidney. The median time of documentation of striped fibrosis in FK506-

FIG. 2. Acute FK506 toxicity resulted in prominent myocyte vacuolation in this interlobular artery. The patient clinically responded to a reduction in the dose of the drug.

treated patients was 200 days (range, 62–406). Striped fibrosis was not always consistently demonstrable in sequential biopsies from the same patient. This can conceivably be a function of the orientation of the biopsy needle in relation to the parallel bands of fibrosis. Alternately, the fibrosis may be focal in its distribution and not always sampled.

Hyalinosis of arterioles and interlobular arteries was noted in 10 biopsies from nine FK506-treated allografts examined 7 to 531 days post-transplant (median, 154 days). Three biopsies were performed within 2 weeks of transplantation and probably reflected donor disease. The remaining seven biopsies were associated with tubular vacuolation (six instances), tubulointerstitial calcifications (four instances), and striped fibrosis (three instances). Because hypertension was not a significant clinical problem in these patients, it is quite likely that FK506 had a role in the pathogenesis of hyalinosis in the latter seven cases, as has been previously reported for cyclosporine (21). Diabetes mellitus can produce similar vascular lesions in the kidney.

Thrombotic microangiopathy associated with hemolytic uremic syndrome developed in one of the FK506-treated patients in this series. It is difficult to attribute unequivocally the syndrome to FK506 therapy, but it is worth recalling that glomerular capillary thrombosis has been observed in association with cyclosporine therapy (13,29,32). The severity of the underlying pathology varies and, as illustrated by the case reported here, the allograft can potentially recover completely from such an insult. However, in other cases focal segmental thickening or reduplication of the segmental glomerular capillary basement membrane, without mesangial interposition, can also ensue (22). A number of fatalities associated with cyclosporine-induced hemolytic uremic syndrome have been recorded (15,31). The differential diagnosis of thrombotic microangiopathy includes other causes of hemolytic syndrome and acute vascular rejection.

The patient with FK506-associated arteriopathy reported here responded to a reduction in drug dosage, and the allograft is functioning well following this presumed toxic episode. We have since also seen another similar mild, self-limited case. Arteriopathy associated with cyclosporine is well documented (13,32). When associated with marked intimal proliferative lesions, it can lead to graft loss (13,32). Milder cases similar to ours have been reported by Mihatsch et al. (23). Experimental toxicology studies, however, have not shown any vascular toxicity of FK506 in the renal arterial tree (1,8,37). It is important to stress that the occurrence of vascular lesions in renal allografts should not always be equated with acute drug toxicity. Indeed we and others (13) believe that acute vascular rejection accounts for most such cases. Before attributing proliferative arteriopathy to drug therapy, one should give due consideration to the possibility that acute humoral (vascular) rejection can occur in lymphocyte crossmatch-negative patients, mediated by antibodies directed to donor endothelial antigens or to other non human leukocyte antigen (HLA) specificities (2).

Focal glomerulosclerosis noted in four patients receiving FK506 also calls for comment. The native kidney disease was essential hypertension in two cases, diabetes mellitus in one case, and undetermined in the remaining case. One biopsy had changes of chronic transplant glomerulopathy and vasculopathy, and focal glomerulosclerosis in this instance could have an ischemic basis. In one case, a crescenteric lesion with mesangial proliferation observed in a previous biopsy suggested de novo glomerulonephritis as the cause of the focal sclerosing lesion in the glomeruli. In the remaining two

(3a)

(3b)

(4)

FIG. 3. (a) A striped pattern of fibrosis with atrophy of the entrapped tubules develops on long-term administration of FK506, as has been reported for cyclosporine. **(b)** Focal calcifications in the tubular epithelium and interstitium accompany the fibrosis.

FIG. 4. Deposition of a hyaline material can be observed in arterioles in patients on FK506 therapy not known to be diabetic or hypertensive. These changes have also been described with cyclosporine therapy (Periodic acid Schiff stain).

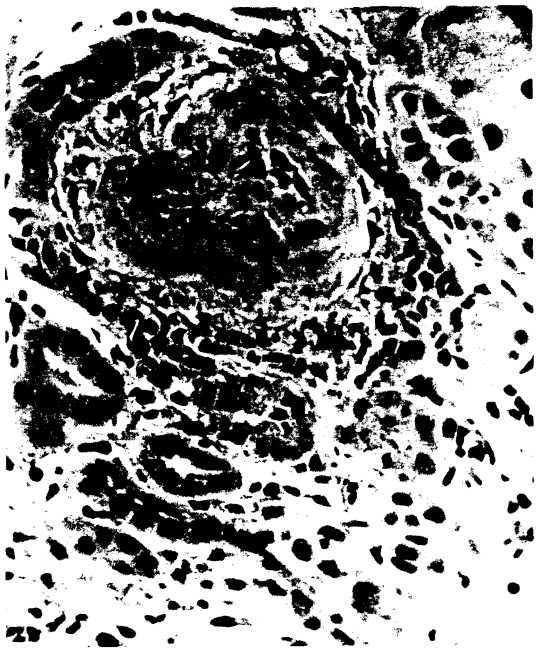

FIG. 5. The interlobular artery shown has fibrin deposition, lymphocytes, and nuclear debris in its media. The renal function tests in the patients improved as the dosage of FK506 was lowered.

cases, concomitant tubular vacuolation, tubulointerstitial calcification, and striped fibrosis raised the possibility that FK506 itself had a role in the development of focal segmental glomerulosclerosis. Consistent with this notion, patterns of proteinuria indicative of glomerular injury have been reported in patients receiving FK506 (7). Focal segmental glomerulosclerosis has been associated with chronic cyclosporine therapy (20); but, in general, glomerular lesions due to immunosuppressive drugs are still poorly understood (22).

The exact mechanism of FK506-induced renal toxicity is not known. A direct antiproliferative effect of the drug on renal proximal tubular cell lines has been shown (17). A reduction of proximal tubule phosphoenolypyruvate carboxylkinase mRNA leading to increased fractional citrate seems to occur in the rat kidney (25). Intrarenal vasoconstriction, possibly mediated by endothelin secretion by glomerular mesangial cells, may also be involved (16). FK506 is chemically unrelated to cyclosporine and has a distinct target receptor. The marked similarity in the morphologic correlates of drug toxicity observed for these two drugs suggests that the ultimate molecular mechanisms involved in cell injury must be closely interlinked. Evidence that these mechanisms may not be totally identical comes from a report that FK506 is an effective replacement immunosuppressant in cases of cyclosporine associated hemolytic uremic syndrome (18). □

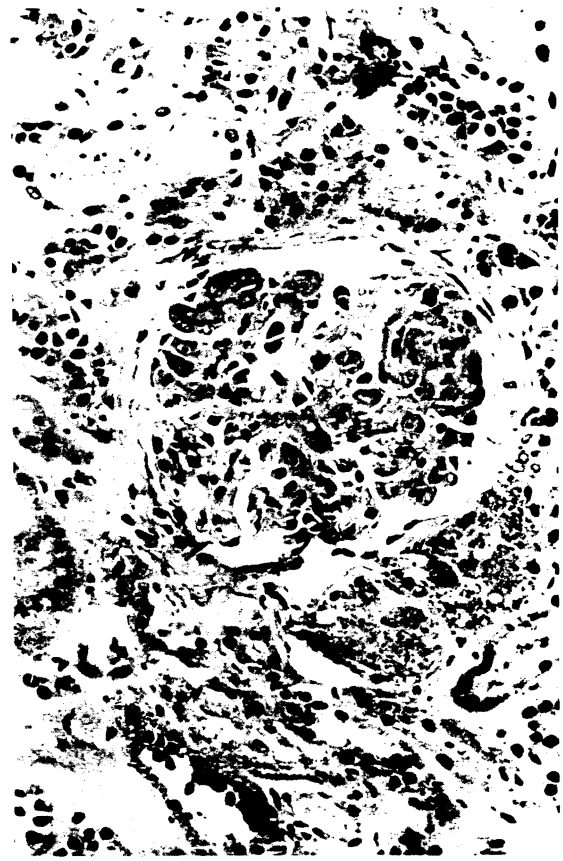

FIG. 6. The glomeruli in this case on FK506 therapy show capillary thrombosis and segmental necrosis. The patient presented clinically as a hemolytic syndrome for which no definite cause could be established.

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