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FK506-ASSOCIATED THROMBOTIC MICROANGIOPATHY

REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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Background. **FK506 is a recently developed immunosuppressant that has been useful in improving the survival of transplanted organs. Among the numerous adverse side effects of FK506, thrombotic microangiopathy (TMA) stands out as an infrequent but severe complication.**

Methods. **We report two cases of FK506-associated TMA and review the 19 previous reported cases.**

Results. **From these 21 cases, the reported incidence of FK506-associated TMA is between 1% and 4.7%. It is more frequent in females, and the mean age at presentation is 47 years. Eighty-one percent of the cases occurred in patients with kidney allografts, and the remaining patients had liver, heart, or bone marrow transplants. Clinically, TMA was diagnosed at an average interval of 9.3 months from the time of transplantation. Patients may be asymptomatic or may present with the full-blown picture of hemolytic uremic syndrome. All patients had an elevated serum creatinine level but did not always show signs of hemolysis. Trough levels of FK506 were not predictive for the development of TMA, but generally a reduction of drug dose correlated with kidney function improvement and disappearance of the hemolytic picture. The renal allograft biopsy provided a conclusive diagnosis in all 17 cases in which this procedure was performed. Treatment, which mainly consisted of reduction or discontinuation of FK506, anticoagulation, and/or plasmapheresis with fresh-frozen plasma exchange, resolved TMA in most patients (57%). However, in one of these patients (5%), the graft was subsequently lost due to causes unrelated to TMA, such as acute or chronic rejection. Despite treatment, one patient (5%) lost the graft due to acute rejection and persistent TMA, and three other patients (14%) who had bone marrow, heart, and liver transplants, died of multiple organ failure, probably unrelated to TMA. In the remaining four patients (19%), response to treatment was not reported.**

Conclusions. **TMA must be considered in organ transplant patients treated with FK506 whenever kidney function deteriorates, even in the absence of microangiopathic hemolytic anemia. Although TMA usually responds to treatment, it may, in rare cases, lead to loss of kidney function or even the patient's death.**

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FK506 is a macrolide lactone, a metabolite of the fungus *Streptomyces* tsukubaensis, that has proved to be a potent immunosuppressant in organ transplantation, effective in preventing the rejection of liver, kidney, small intestine, heart, and pancreatic islet tissue allografts (*1*, *2*). Nephrotoxicity is the most common adverse effect of FK506, with an incidence ranging between 17% and 44% (*2*, *3*). FK506 nephrotoxicity can be classified into two broad categories, i.e., functional and structural. Functional toxicity includes hyperkalemia, hypomagnesemia, hypertension, and renal dysfunction associated with vasoconstriction (*4*). Kidney biopsy specimens in patients with functional FK506 nephrotoxicity do not show any significant changes. Structural nephrotoxicity can be acute or chronic (*5*): acute nephrotoxicity is usually characterized by marked tubular changes including isometric vacuolization of tubular cell cytoplasm, giant mitochondria, and microcalcification. However, microvascular changes involving arterioles or glomerular capillaries may sometimes predominate, and display a wide spectrum of severity, ranging from mild, nonspecific lesions such as apoptosis and vacuolization of medial smooth muscle cells to TMA. Chronic nephrotoxicity is characterized by chronic tubulointerstitial damage, glomerulosclerosis, and hyalin or fibromucoid thickening of the arteriolar wall (*2*, *5*).

TMA is a rare but dangerous and well-documented phenomenon in organ transplantation after FK506 administration. Since the first report by Schmidt et al. in 1991 (*6*), 18 more cases have been documented. We present two more cases of FK506-associated TMA after kidney transplantation and review its epidemiology, clinical manifestations, renal biopsy findings, therapeutic options, and prognosis.

MATERIALS AND METHODS

From a MEDLINE database computerized search between the years 1990 and 1998, 19 reported cases of FK506-associated TMA in the English language were found. We also reviewed the records of all patients with kidney or kidney-pancreas transplants performed at The Methodist Hospital, who were treated with FK506. There were, in a 3-year period between 1994 and 1997, 54 such patients, among which 2 cases of biopsy-proven FK506-associated TMA were found.

Case Reports

Our two cases will be presented first, followed by the data extracted from the previous reports in the literature.

Case 1. A 38-year-old Caucasian man received a kidney-pancreas transplant for end-stage diabetic nephropathy. After initial induction with OKT3 and high-dose methylprednisolone, posttransplantation immunosuppression consisted of methylprednisolone at 30 mg/day, tapered down to 10 mg/day by 2 months, azathioprine at 150

mg/day, and FK506 at 5 mg/day. Clinical improvement was achieved shortly after transplantation and was characterized by a baseline serum creatinine (Scr*) level of 1.4 mg/dl and a fasting glycemia of 102 mg/dl. Three months later, the renal function deteriorated, with a peak Scr level of 3.1 mg/dl.

After a renal allograft biopsy showing early acute cellular rejection, the patient was treated with high-dose steroids and OKT3 (total dose 30 mg), and azathioprine was changed to mycophenolate mofetil (2 g/day). The Scr level dropped to 2.7 mg/dl, but 2 weeks later it increased to 4 mg/dl. A second allograft biopsy disclosed tubular calcification and vacuolization, consistent with FK506 tubulotoxicity. FK506 was changed to cyclosporine (CsA) 225 mg b.i.d., resulting in a decrease of Scr level to 2.5 mg/dl.

Seven months after transplantation, kidney function again deteriorated. Laboratory studies showed the following levels: white blood cell count (WBC) 3,700/mm^3; hematocrit 45%; hemoglobin 15.7 g/dl; platelets 223,000/mm^3; blood urea nitrogen (BUN) 39 mg/dl; Scr 4.2 mg/dl; and glycemia 87 mg/dl. A third allograft biopsy showed features consistent with CsA-induced chronic nephrotoxicity, including hyalin or myxoid thickening of arteriolar walls, and a striped type of tubular atrophy and interstitial fibrosis. In addition, acute thrombosis involving some glomerular capillaries and arterioles was also noted, raising the possibility of CsA-associated TMA. There were no features of antibody- or cell-mediated rejection. CsA was replaced by FK506 (8 mg/day) and warfarin was started at 2.5 mg/day. The renal function improved, and the patient did well for the following 6 months, with his Scr level ranging between 2.9 and 3.2 mg/dl.

Thirteen months after transplantation, he became weak, lethargic, and anorectic. His physical examination was unremarkable except for a fever of 39.2°C. Laboratory studies showed the following levels: WBC 3,900/mm^3; hematocrit 45%; hemoglobin 15 g/dl; platelets 62000/mm^3; lactate dehydrogenase (LDH) 878 U; BUN 116 mg/dl; Scr 6.6 mg/dl; glycemia 68 mg/dl; sodium 137 mEq/L; potassium 5.9 mEq/L; and chloride 119 mEq/L. Chest x-ray, urinary culture, and peripheral blood cultures were negative. A peripheral blood smear showed diminished platelets and many schistocytes. A whole blood level of FK506 was 15 ng/ml. A fourth renal allograft biopsy showed chronic tubulointerstitial damage and arteriolar changes consistent with chronic CsA and/or FK506 nephrotoxicity; in addition, focal glomerular and arteriolar acute thrombosis was noted. This finding, together with the clinical presentation, raised the possibility of FK506-associated TMA (Fig. 1, A–C). Features of antibody- or cell-mediated rejection were not present. Treatment included reducing FK506 to 2.5 mg b.i.d. and mycophenolate to 500 mg/day, plasmapheresis, and replacement with fresh-frozen plasma. Platelet count increased to 144,000/mm^3, his BUN dropped to 38 mg/dl, and his Scr level dropped to 3.2 mg/dl.

Sixteen months after transplantation, his kidney function declined again with a peak Scr level of 5.1 mg/dl. A fifth allograft biopsy showed chronic transplant nephropathy and moderate acute cellular rejection. Whether the chronic transplant nephropathy was due to chronic rejection, to CsA or FK506 chronic nephrotoxicity, or to a combination of these factors cannot be determined with certainty. There were no features of TMA. He underwent a 14-day course of intravenous antithymocyte globulin, and FK506 was diminished to 1.5 mg b.i.d. (trough whole blood level 12 ng/ml). His kidney function has remained stable for the past 6 months, with a baseline Scr level of 4.8 mg/dl.

Case 2. A 30-year-old Caucasian woman with renal failure secondary to lupus nephritis received a cadaveric kidney transplant. Her immunosuppression consisted of methylprednisolone at 30 mg/day, mycophenolate mofetil at 1 g b.i.d., and FK506 at 5 mg b.i.d. Shortly after transplantation, the Scr level decreased to 1.7 mg/dl. Two weeks later, the Scr level rose to 3.8 mg/dl. A renal allograft

* Abbreviations: BUN, blood urea nitrogen; CsA, cyclosporine; LDH, lactate dehydrogenase; Scr, serum creatinine; TMA, thrombotic microangiopathy: WBC, white blood cell count.

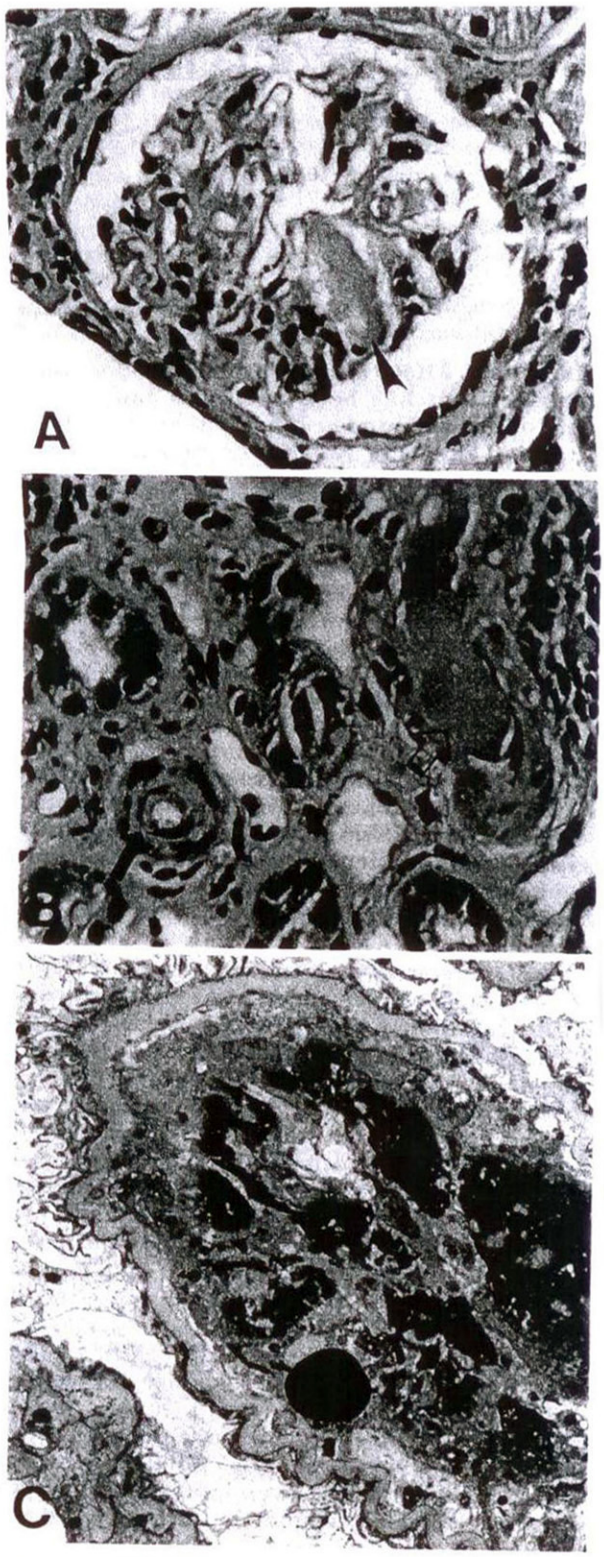

FIGURE 1. Case 1. The fourth renal transplant biopsy showing both thrombotic microangiopathy and features suggestive of chronic FK506 toxicity. (A) A thrombus (arrowhead) is present in a glomerular capillary (hematoxylin-eosin, ×1980). (B) A thrombus is noted in the lumen of an arteriole (arrowhead). Another arteriole displays fibrous intimal thickening (arrow). There are also tubular atrophy and interstitial fibrosis (hematoxylin-eosin, ×1980). (C) Electron microscopic study confirms the presence of fibrin platelet thrombi in glomerular capillaries (electron microscopy, ×8000).

biopsy showed mild and predominantly cellular acute rejection. She was treated with OKT3 (total dose 50 mg), and the Scr level dropped to 2.2 mg/dl.

Thirteen months after transplantation, she developed proteinuria and worsening of kidney function. The patient was asymptomatic, and the physical examination was unremarkable. Laboratory studies showed the following levels: WBC 5,600/mm^3; hematocrit 39%; hemoglobin 12.4 g/dl; platelets 194,000 mm^3; BUN 39 mg/dl; Scr 3.8 mg/dl; LDH 199 U; sodium 133 mEq/L; potassium 4.4 mEq/L; and protein excretion 1.32 g/day. Complement levels were within normal limits and anti-DNA was positive 1:80. Repeated peripheral smears showed no schistocytes. An FK506 whole blood level was 12 ng/ml. A second allograft biopsy displayed changes consistent with FK506 chronic toxicity, including patchy tubular atrophy, interstitial fibrosis, and circumferential hyalin deposition in arteriolar walls. In addition, acute thrombosis involving a few glomerular capillaries and arterioles were noted, raising the possibility of FK506-associated TMA (Fig. 2, A–C). Histologic patterns of recurrent lupus lesions were not found in the biopsy specimen by immunofluorescence and electron microscopy. FK506 was replaced by CsA at 200 mg b.i.d., and warfarin at 2.5 mg/day was started. On this regimen, she improved with the platelets rising to 213000/mm^3, the BUN dropping to 35 mg/dl, and the Scr level dropping to 2.6 mg/dl; tests for lupus anticoagulant and anticardiolipin antibodies were negative.

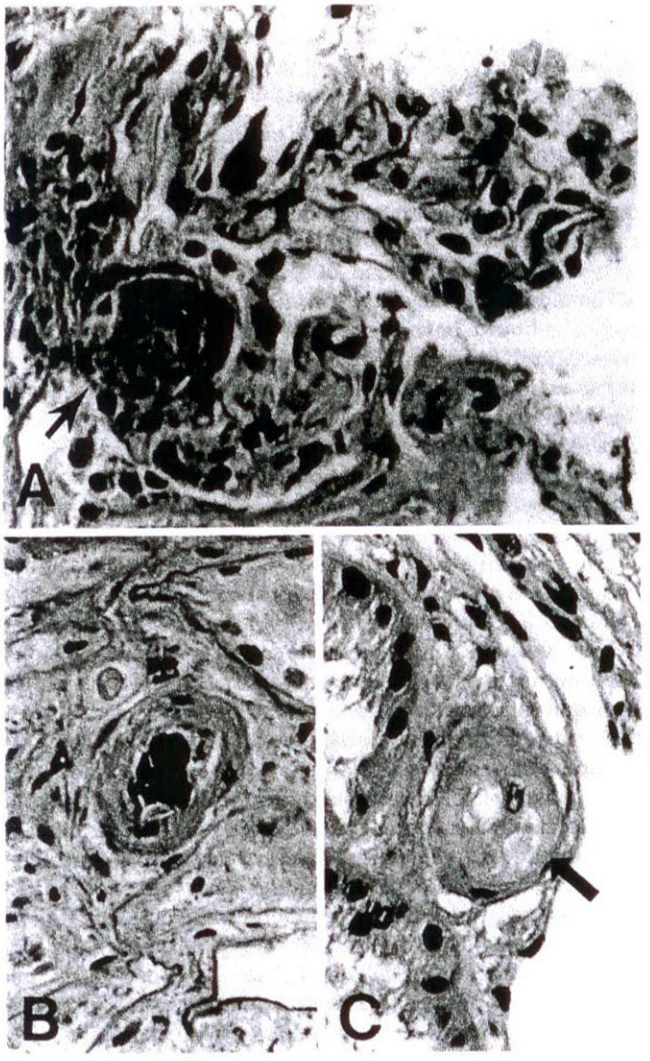

FIGURE 2. Case 2. The second renal transplant biopsy showing features of thrombotic microangiopathy. (A) A glomerular thrombus (arrowhead) is present (hematoxylin-eosin, ×1980). (B) Acute thrombosis involving arterioles (Masson's trichrome, ×1980). (C) Nonspecific changes involving an arteriole, including hyalin deposits in the vascular wall and vacuolization of endothelial cells (hematoxylin-eosin, ×1980).

Sixteen months after transplantation, her Scr level again rose to 4.8 mg/dl. A third graft biopsy disclosed changes consistent with FK506 chronic nephrotoxicity, including severe tubular atrophy, interstitial fibrosis, and marked thickening of arterial walls, but interstitial inflammation was scanty. The immunosuppression regimen was not changed. Her kidney function continued to deteriorate, and a transplant nephrectomy was performed 18 months after transplantation. The removed renal allograft showed a spectrum of changes similar to, but more severe than, those noted in the third biopsy.

Review of literature. We have found 19 cases of FK506-associated TMA since the first description by Schmidt et al. in 1991 (*6*). The features of these cases and the two current ones are summarized in Table 1. Although in many of these cases the reported data are incomplete for the purposes of this analysis, some observations on FK506-associated TMA can be made. The mean age at presentation was 47.7±16.2 years (range, 29–76 years); the female to male ratio was 1.4:1 (sex was indicated in 15 of 19 patients). Most of the cases (15 of 19; 78.9%) were reported in kidney transplant recipients, whereas recipients of liver, heart, and bone marrow transplants accounted for 10.5%, 5.3%, and 5.3% of cases, respectively (*9–11*). The disorders that led to failure of the native organs were undetermined in five cases (26.3%); diabetes mellitus in three (15.8%); systemic lupus erythematosus in two (10.5%); cirrhosis in two (10.5%); glomerulonephritis in two (10.5%); and polycystic kidney disease, renal tubular acidosis, IgA nephropathy, acute lymphocytic leukemia, and alcoholic cardiomyopathy in one (5.3%) each. The time from transplantation to the onset of TMA, although not always specified, was 9.3±7.9 months (range, 4 days to 31 months). FK506 dose at time of diagnosis varied between 8 and 45 mg/day, and the trough levels (when specified) were in the accepted therapeutic range, with the exception of one, which was markedly high (*7*).

When reported, the clinical presentation was variable and ranged from an absence of systemic symptoms or signs of hemolysis (*7*) to the florid picture of hemolytic anemia, azotemia, and thrombocytopenia (*6, 7, 9–11*). When mentioned, LDH levels were elevated in only 6 cases (*6, 7, 9–11*), but schistocytes were invariably present (19 cases). One renal transplant patient presented with nephrotic syndrome and hemolytic anemia 4 days after the transplantation, and no features of rejection in the allograft biopsy were mentioned (*2*). Renal function at presentation, reported in 15 patients (11 kidney, 2 liver, 1 heart, and 1 bone marrow transplant) was abnormal in each case, with a Scr level ranging from 1.6 to 6.6 mg/dl. Renal allograft biopsy was performed in 15 patients (*2, 3, 6-8*), all of whom were renal transplant recipients, and in each case, displayed acute thrombi within the glomerular capillaries and/or arterioles. Acute rejection was not seen in any of these transplant biopsies, and features of chronic transplant nephropathy were not mentioned in any case. Interestingly, in all four remaining patients whose transplanted organs were not kidneys, a renal biopsy was not performed and the diagnosis of TMA was made on clinical grounds alone (*9–11*). In one of them, despite treatment, the hemolytic picture persisted and the patient died; the diagnosis of TMA in this patient was confirmed at autopsy (*11*). In the other three patients, the clinical diagnosis of TMA was supported by improvement after appropriate treatment (*9, 10*).

Treatment was reported in 18 of 19 patients. In nine patients (47.3%), all with renal transplants, simply decreasing the dose of FK506 was followed by an improvement in kidney function and disappearance of the hemolytic picture (*3, 7*). However, in three of these patients, reducing the dose of FK506 was followed by acute cellular rejection approximately 3 months after the diagnosis of TMA. There was no evidence of capillary thrombi in the kidney

TABLE 1. Data related to FK506-associated TMA: summary of the reported cases[a]

Case	Age (yr)	Sex	Transplant organ	Original disease	Time to TMA (mo)	FK506 dose	Scr level (mg/dl)	Frequency (%)	Treatment	Outcome	Ref.
1	36	F	Kidney	SLE	8	12 mg/day	3.3	?	Pl, Fp, stop FK	Good	6
2	27	F	Bone marrow	ALL	23	0.3 mg/kg	1.6	?	Pl, Fp, W, stop FK	Death	11
3	32	F	Liver	Cirrhosis	11	8 mg/day	2.3	?	Pl, Fp, reduce FK	Good	9
4	?	?	Kidney	?	1	0.1 mg/kg	?	1.4	?	?	2
5	36	F	Kidney	SLE	9	14 mg/day	4.6	1.9	Stop FK	?	7
6	29	F	Kidney	?	<1	20 mg/day	3	1	Reduce FK	Good	7
7	54	M	Kidney	IgA	1.5	45 mg/day	2.5	1	Reduce FK	Good	7
8	75	M	Kidney	PKD	<1	18 mg/day	6.1	1	Reduce FK	Good	7
9	47	F	Kidney	DM	1.5	10 mg/day	3.1	1	Reduce FK	Good	7
10	51	F	Kidney	DM	3.5	36 mg/day	2.2	1	Reduce FK	Good	7
11	76	M	Kidney	GN	<1	20 mg/day	8.0	1	Reduce FK	Graft loss	7
12	21	M	Kidney	RTA	18	12 mg/day	4.0	1	Reduce FK	Good	7
13	33	F	Kidney	GN	8	10 mg/day	1.7	1	Reduce FK	Good	7
14	60	F	Kidney	DM	2.5	12 mg/day	4.3	1	Reduce FK	Good	7
15	53	M	Heart	CHF	19	12 mg/day	2.4	?	Pl, Fp, stop FK	Death	10
16	62	M	Liver	Cirrhosis	4	?	2.7	?	Pl, Fp, stop FK	Death	10
17	?	?	Kidney	?	?	0.15 mg/kg	?	4.7	Reduce FK	Good	3
18	?	?	Kidney	?	?	0.15 mg/kg	?	3.3	Reduce FK	?	8
19	?	?	Kidney	?	?	?	?	3.3	Reduce FK	?	8
20	38	M	Kidney	DM	14	8 mg/day	6.6	3.7	Pl, Fp, W	Good	Pr
21	30	F	Kidney	SLE	14	10 mg/day	3.8	3.7	Stop FK, W	Graft loss	Pr

[a] Abbreviations used in table: ALL, acute lymphocytic leukemia; CHF, chronic heart failure; DM, diabetes mellitus; F, female; FK, FK506; Fp, fresh-frozen plasma; GN, glomerulonephritis; M, male; PKD, polycystic kidney disease; Pl, plasmapheresis; Pr, present report; RTA, renal tubular acidosis; SLE, systemic lupus erythematosus; W, warfarin; <1, less than 1 month.

[b] Outcome: Good=patient and graft survived; Death=patient's death due to sepsis and multiple organ failure.

allograft biopsies done at that time (*7*). In one patient with a renal transplant (5.3%), a reduction of the FK506 dose was followed by the loss of the graft, and the graft nephrectomy showed moderate acute cellular rejection and persistent TMA. FK506 was discontinued in three patients, all with renal transplants; in one of these patients (5.3%), discontinuation of FK506 was followed by disappearance of the TMA (*7*), whereas in the other two (10.5%), the outcome was not reported (*8*). The five remaining patients (26%) were treated with plasmapheresis, fresh-frozen plasma exchange, high-dose steroids, anticoagulation, and a decrease or discontinuation of FK506 (*6, 9-11*). Three of these patients, who had a liver, a heart, and a bone marrow transplant, died of sepsis and multiple organ failure (*10, 11*). Kidney function recovered in the remaining two (one liver and one renal transplant recipient) (*6, 9*).

DISCUSSION

FK506-associated TMA is a well-documented and severe, albeit rare, cause of renal failure in organ transplantation. This entity has been described in kidney (*2, 3, 5–8*), liver (*9, 10*), heart (*10*), and bone marrow (*11*) transplant recipients.

The diagnosis of FK506-associated TMA in the two patients who are the subject of the present report, was supported by both renal biopsy findings and clinical follow-up. Two episodes of TMA occurred in the first patient. The first episode of TMA, characterized by an elevated Scr level, absence of laboratory signs of intravascular hemolysis, and acute microvascular thrombosis, was probably due to CsA, because the patient was receiving CsA at that time, and replacing CsA with FK506 was associated with improvement of renal function. The second episode of TMA, which occurred 6 months later and most probably was due to FK506, was more typical and characterized by acute renal failure, thrombocytopenia, schistocytes, elevated serum LDH, and microvascular thrombosis on renal allograft biopsy. It should be noted, however, that anemia was not present and the whole blood FK506 level was within the therapeutic range. The diagnosis of FK506-associated TMA was also supported by the significant improvement in renal function after a reduction in the dose of FK506 and treatment with plasmapheresis.

In the second patient, the episode of FK506-associated TMA was characterized by a sudden decrease of renal function in the absence of features of intravascular hemolysis, normal serum LDH, and therapeutic whole blood levels of FK506. The diagnosis of TMA was raised only by microvascular thrombosis noted in the allograft biopsy. This diagnosis was also supported by the observation that although reducing the dose of FK506 was not associated with improvement, switching to CsA restored the renal function to baseline.

Most cases of FK506-associated TMA have been described in renal transplant patients, with a frequency of about 1% (*7*). It should be noted that TMA has also been reported as a complication of CsA, with a frequency of about 3% (*12*). In our experience, of a total of 149 kidney or combined kidney-pancreas transplants from 1994 to 1997 (the period of time we have been using FK506), FK506 has been used in 54 patients; in 15 of them a kidney transplant biopsy was performed due to renal dysfunction, and TMA was diagnosed in 2 cases (3.7%). FK506 was preferentially used in female transplant recipients, when a history of severe hypertension was present, or as a rescue therapy replacing CsA. Over the same time frame, 90 patients received CsA, and TMA was diagnosed in 6 kidney transplant biopsy specimens (5.5%). It should be noted that in the context of organ transplantation, glomerular capillary and arteriolar thrombi can be seen not

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SAFETY OF KIDNEY BIOPSY IN PEDIATRIC TRANSPLANTATION

A REPORT OF THE CONTROLLED CLINICAL TRIALS IN PEDIATRIC TRANSPLANTATION TRIAL OF INDUCTION THERAPY STUDY GROUP[1,2]

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Background. **Historically, young children undergoing renal transplantation have lower allograft survival than adults, and potential causes of this are being addressed by the North American Pediatric Renal Transplant Cooperative Study through the National Institutes of Health-sponsored study Cooperative Clinical Trials in Pediatric Transplantation. Included in this study is evaluation of surveillance renal biopsies (SB) and clinically indicated biopsies (CB). Few data exist in children to identify the risk involved with renal transplant biopsies.**

Methods. **Questionnaires were mailed to 21 participating centers asking for descriptions of adverse events associated with kidney biopsies, with choices limited to none, gross hematuria, perinephric hematoma, and other. Further clinical details were obtained from review of medical records of all patients with reported adverse events. Data were collected from 19 centers on 126 patients.**

Results. **Eighty-six patients had undergone 212 biopsies (75 SB and 137 CB). Nine biopsy-related adverse events were reported (4.2%): three SB (4.0%) and six CB (4.4%). Gross hematuria was reported in six patients (2.8%): two SB (2.7%) and four CB (2.9%). A perinephric hematoma was reported in one patient. Two patients with intraperitoneal kidneys developed significant bleeding after biopsy and required transfusions and surgical exploration. No patient lost kidney function or required nephrectomy after biopsy. No difference was noted in adverse events between SB at day 5 or 12 versus CB.**

Conclusion. **Evaluation of transplanted kidney tissue may provide important information for the care of the transplantation patient. This analysis suggests that transplanted kidney biopsies can be performed with minimal risks in pediatric patients.**

Renal transplantation has become the treatment of choice for children with end-stage renal disease. Growth, development, and quality of life are markedly improved after transplantation compared with other forms of renal replacement therapy (*1*). However, in spite of improved surgical techniques, immunosuppressive medicines, and medical care, both patient and allograft survival for patients 0–4 years of age remains significantly less than that seen in adults. The United Network of Organ Sharing's 1996 annual report

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