Cholesterol Emboli Presenting as Acute Allograft Dysfunction After Renal Transplantation1

Inderjit Singh, Paul D. Killen, and Alan B. Leichtman2

ABSTRACT
Cholesterol emboli are a common complication of atherosclerotic vascular disease. A 40-yr-old renal transplant recipient who developed acute allograft dysfunction 1 day after the initiation of cyclosporine therapy and 6 days after transplantation is described. A renal allograft biopsy revealed cholesterol emboli in interlobular arteries and in glomeruli. Four previously reported cases of cholesterol emboli in renal allografts are described, and the cause and pathogenesis of atheroembolic disease are reviewed. Atheroemboli causing injury to the renal allograft may arise from either donor or recipient vessels. Vigilance for the occurrence of these emboli needs to be maintained when donor or recipient vessels demonstrate evidence of significant atherosclerotic vascular disease.

Key Words: Atheroemboli, cholesterol emboli, cyclosporine, vasculopathy, renal transplant

A 40-yr-old man who had developed ESRD presumed to be secondary to chronic glomerulonephritis received a one A, one B, one DR matched
Cholesterol Emboli in Renal Allografts

Cadmver renal transplant on October 30, 1992, at the University of Michigan Medical Center. He had been maintained on continuous ambulatory peritoneal dialysis since June 1989. He had a history of alcohol abuse and alcoholic cirrhosis but denied current or recent alcohol ingestion, and his liver function tests, including synthetic function, were within normal limits. There was no known history of diabetes, hypertension, hypercholesterolemia, or atherosclerotic coronary artery or peripheral vascular disease.

The donor was a 54-yr-old male smoker with a 1-yr history of myocardial infarction and one-vessel angioplasty. His death was attributed to a cerebrovascular accident. Warm ischemia time was recorded as 30 min, and cold ischemia time was recorded as 9.5 h.

His care followed the standard University of Michigan Medical Center Cadaver Renal Transplant Protocol. He received “quadruple therapy,” with ATGAM® (The Upjohn Company, Kalamazoo, MI), prednisone, and azathioprine induction (Figure 1). By the fifth postoperative day, his creatinine had improved to 2.2 mg/dL and cyclosporine (Sandimmune®: Sandoz Pharmaceuticals Corporation, East Hanover, NJ) was initiated. His only additional medications at the time of cyclosporine initiation were one dose per day of trimethoprim-sulfamethoxazole DS, and 200 mg of acyclovir thrice daily.

His creatinine began to rise on the sixth postoperative day. On the 11th postoperative day, his creatinine was 6.6 mg/dL, blood urea nitrogen was 83 mg/dL, magnesium was 1.6 mg/dL, white blood cell count was 7,300 cells/μL, hemoglobin was 9.0 g/dL, and hematocrit was 25.1%. Urinalysis demonstrated zero to three white blood cells per high-power field, zero to three red blood cells per high-power field, 30 mg/dL protein, and an occasional granular cast. The 24-h, whole-blood, trough cyclosporine level by HPLC was 163 ng/mL. His blood pressure was 160/80 mm Hg, and his temperature was 98.8°F. Examination of the lungs, cardiovascular system, abdomen, central nervous system, and extremities was unremarkable. An open renal biopsy was performed.

The biopsy of renal cortex and superficial medulla revealed scattered foci of infarction, characterized by

![Figure 1. Relationship between 24-h cyclosporine (cyclosporin A) trough level and serum creatinine over 80 days after transplantation. Upper panels represent other immunosuppression received over the same time period. Arrow indicates day of biopsy.](image)
Coagulative necrosis of tubules, interstitial edema, and acute interstitial inflammation. Several thrombosed glomeruli contained small cholesterol emboli. Other glomeruli demonstrated focal proliferation of epithelial cells in Bowman’s space associated with segmental thrombosis. The vessels demonstrated moderate fibrous intimal thickening and medial sclerosis. Superimposed on these chronic changes was embolization of interlobular-sized vessels with cholesterol, which evoked reactive intimal proliferation and focal thrombosis. There was no evidence of rejection or tubular injury (Figure 2).

He had not been anticoagulated or undergone any invasive vascular procedures after transplantation. Careful reexamination failed to reveal any systemic manifestation of cholesterol embolization (CE) including rash, livedo reticularis, or Hollenhorst plaques. Complement levels were within normal limits, and there was no eosinophilia or eosinophiluria. The other kidney from the same donor had been transplanted at another institution into a 47-yr-old, otherwise healthy man. The male allograft was never biopsied, but suffered primary nonfunction that began to resolve on the 17th postoperative day. The harvesting surgeons had noted a calcified atherosclerotic plaque in the abdominal aorta of the donor but had judged the renal arteries to be uninvolved.

Because it was possible that cyclosporine-induced intrarenal vasoconstriction, arterioloapathy, or platelet aggregation may have contributed to the vascular insult, the cyclosporine dose was reduced to achieve trough levels between 60 and 90 ng/ml. No other modification in this therapeutic regimen was undertaken, and over the next 2 months, he achieved a stable baseline creatinine of 2.1 mg/dL (Figure 1).

CAUSE, PATHOGENESIS, AND CLINICAL FEATURES

CE is a multisystem disorder that may involve the skin, muscle, kidneys, spleen, gastrointestinal tract, and central nervous system (1). It most frequently affects elderly men with evidence of diffuse atherosclerotic vascular disease (1–3). The signs and symptoms of CE are nonspecific, range from mild to severe, and in addition to evidence of end-organ injury, include fevers, rash, weight loss, myalgias, headaches, leukocytosis, eosinophilia, hypocomplementemia, and an elevated erythrocyte sedimentation rate. The illness is often confused with polyarteritis nodosa, polymyositis, small vessel vasculitis, subacute bacterial endocarditis, or left atrial myxoma (4,5).

CE is a common complication of atherosclerotic plaques and follows ulceration of the fibrous cap, which exposes the cholesterol matrix to the arterial...
Circulation. Cholesterol crystals may, then, enter the circulation spontaneously (6) or dislodge as a result of a variety of inciting factors including angiographic procedures (7), vascular surgery (8), or the use of anticoagulants (9). End-organ damage results from embolization to distal capillaries and small arterioles.

Cholesterol crystals trigger a characteristic localized inflammatory and endothelial reaction. In the first 24 to 48 h, mononuclear cell infiltration and giant cell formation occur and result in the engulfment of the cholesterol crystals. Within 2 to 7 days, endothelial proliferation with intravascular fibrosis develops (10). These crystals are resistant to the scavenger effects of macrophages and may be identified intravascularly after many months (10,11). The inflammatory response to the cholesterol emboli may contribute to many of the systemic manifestations of this disease.

Atheromatous plaque in the abdominal aorta is the source of emboli in the majority of nontransplant-associated cases. The proximity of the renal arteries to the atheromatous aorta and their large blood flow render the kidneys especially vulnerable to CE. The frequency of renal involvement as determined by autopsy depends on the extent of atherosclerotic vascular disease. In one autopsy series, evidence of renal CE was present in 0 to 4% of patients with minimal atherosclerosis, 7 to 30% of patients with severe atherosclerosis or abdominal aortic aneurysm, and 77% of patients undergoing aneurysmectomy (8). Jones and Iannaccone reported evidence of CE in 1% of consecutive renal biopsies in living patients who had unexplained deterioration of renal function (12).

Classically, patients suffer an acute or subacute deterioration of renal function that may be associated with accelerated hypertension, flank or back pain, and concurrent evidence of embolization to other visceral, central nervous system, or cutaneous sites. The characteristic histologic findings are similar to those reported in our patient, but necrotizing glomerulonephritis with crescent formation has also been reported (13). Urinary abnormalities may include mild proteinuria, although nephrotic-range proteinuria has been described, microscopic hematuria, leukocythuria, eosinophiluria, and hyaline or granular casts. Patients are not usually oliguric, and a low fractional excretion of sodium has not been reported, even though the entity is associated with significant renal hypoperfusion.

The treatment of CE in most patients is disappointing. Anticoagulants have been tried (3,14) but may lead to further injury by preventing the organization of thrombus over an ulcerated plaque. Systemic corticosteroids may reduce the inflammatory response in patients whose clinical course resembles systemic vasculitis. Low-molecular-weight dextran, systemic vasodilators, and sympathetic blockers have all been tried without effect. In patients with renal failure, dialytic support is sometimes necessary (15,16).

Although a minority of patients may ultimately recover, the overall prognosis is poor and prevention remains critical. Fine et al. (1) found a 73% mortality rate in a retrospective review of all reported cases of CE. Attempts to reduce the incidence of CE in high-risk patients include gentle handling of involved vessels, complete replacement of the atherosclerotic segments during vascular surgery, and the avoidance of stiff catheters and high-pressure injections during arteriography in patients with known peripheral vascular disease.

**CHOLESTEROL EMBOLI IN RENAL ALLOGRAFTS**

Very little has been written about CE-related renal allograft dysfunction. To the best of our knowledge, only four cases have been reported. These cases have been summarized in Table 1. Pirson et al. (17) described a 56-yr-old woman, 19 yr postcadaveric renal transplant, who was maintained on azathioprine and prednisone with a serum creatinine of 2.0 mg/dL. After an acute myocardial infarction, he was treated with intravenous streptokinase and heparin infusion. He subsequently developed progressive renal insufficiency, and his serum creatinine rose to 6.4 mg/dL. A percutaneous renal biopsy, 17 days after the myocardial infarction, confirmed CE. Allograft function improved gradually over a period of 7 months to a baseline serum creatinine of 2.5 mg/dL. Ultrasound of the aorta and coronary angiography revealed diffuse atherosclerosis.

Jennings et al. (18) described a 46-yr-old woman, 7 yr postcadaveric renal transplant, who presented with

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age of Patient (yr)</th>
<th>Time Posttransplant</th>
<th>Probable Origin of Emboli</th>
<th>Probable Inciting Event</th>
<th>Outcome</th>
<th>Nature of Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirson et al. (17)</td>
<td>56</td>
<td>19 yr</td>
<td>Native aorta</td>
<td>Thrombolytic therapy for acute myocardial infarction</td>
<td>Partial recovery</td>
<td>Systemic</td>
</tr>
<tr>
<td>Jennings et al. (18)</td>
<td>46</td>
<td>7 yr</td>
<td>Native iliac artery</td>
<td>Deceleration injury</td>
<td>Partial recovery</td>
<td>Renal limited</td>
</tr>
<tr>
<td>Aujla et al. (19)</td>
<td>64</td>
<td>1.5 yr</td>
<td>Native abdominal aorta</td>
<td>Unknown</td>
<td>Complete recovery</td>
<td>Systemic</td>
</tr>
<tr>
<td>Aujla et al. (19)</td>
<td>27</td>
<td>Immediate</td>
<td>Donor renal arteries</td>
<td>Harvesting and transplantation</td>
<td>Allograft loss</td>
<td>Renal limited</td>
</tr>
</tbody>
</table>
a traumatic fracture of her wrist and ankle requiring closed reduction. Her serum creatinine rose to 3.1 mg/dL over the next 72 h. A renal biopsy showed many arterioles containing cholesterol clefts. The authors speculated that sudden deceleration during trauma led to disruption of and embolization from an atheromatous plaque in the native iliac artery.

The third patient, who received a second cadaveric renal transplant in April 1985, was a 64-yr-old man with known coronary artery disease. In October 1986, he presented with pain and livedo reticularis of his lower extremities and a nonhealing ulcer on his great toe. Twenty-four-hour urine protein excretion was 10 g. A percutaneous renal biopsy revealed characteristic cholesterol clefts, and a computed tomographic scan of the abdomen demonstrated atheromatous plaques in the abdominal aorta. Serum creatinine peaked at 1.8 mg/dL and gradually returned to its previous baseline of 1.5 mg/dL over the ensuing 3 months (19).

The same authors described a 27-yr-old man with no evidence of atherosclerosis who developed primary nonfunction after a cadaveric renal transplant in August 1987. An allograft biopsy showed that the interlobular arteries exhibited fibrous intimal thickening and that one contained a cholesterol cleft. The donor was a 57-yr-old man with atheromatous plaques involving both the renal arteries and the aorta. This patient’s clinical scenario resembles that of our patient (19).

DISCUSSION

Our patient was a relatively young man with no evidence of atherosclerotic vascular disease. The donor was an older man with a history of cigarette use, hypertension, hyperlipidemia, and coronary artery disease who died from a cerebrovascular accident. The donor’s aorta or renal artery was the likely source of the CE. Plaque could have been dislodged during harvesting, transplantation, or intraoperative anticoagulation. Alternatively, the cerebrovascular accident itself may have been a manifestation of systemic CE, and the renal CE may have occurred before organ procurement.

Cyclosporine toxicity can be functional, without histopathologic alterations or associated with vascular or tubulointerstitial pathology (20). Functional toxicity may be from increased vascular resistance (21) secondary to afferent arteriolar vasoconstriction (22) or to decreased glomerular capillary ultrafiltration (23). Vascular lesions show evidence of arteriolopathy with nodular protein deposition in the arteriolar wall and with mucoid thickening of the intima, causing narrowing or obliteration of the lumen (20). The resulting ischemia may lead to tubular atrophy and interstitial fibrosis. An acute vascular lesion less frequently seen is one that clinically and histologically resembles hemolytic uremic syndrome: glomerular microvascular thrombosis with platelet and fibrin thrombi accompanied by thrombocytopenia and microangiopathic hemolysis (24). Cyclosporine tubulopathy includes giant mitochondria, isometric tubular vacuolization, and microcalcification (20).

It is intriguing to speculate on the relative contributions of cholesterol emboli and cyclosporine nephrotoxicity to this patient’s clinical course. The clinical data are consistent with several alternatives. It is probable that the atheroembolization occurred before or at the time of harvest; however, because the patient’s creatinine improved steadily after transplantation, it is additionally likely that the cholesterol emboli expressed little if any early clinical effect. Furthermore, it is notable that renal function began to deteriorate with the introduction of cyclosporine and improved once more when the daily cyclosporine dose was reduced. Although uncommon, renal function may deteriorate profoundly solely on the basis of cyclosporine-induced physiologic changes (20). It is additionally possible that characteristic cyclosporine-induced tubular or vascular nephrotoxicity might have become apparent on a repeat biopsy. Early functional recovery in patients with CE has also been reported (25). It may be that immunosuppression posttransplantation promoted this recovery by reducing the inflammatory component that accompanies atheroembolic injury. The subsequent deterioration of renal function may have been from cyclosporine-induced renal injury superimposed on atheroembolic injury, which improved consequent to the reduction in the daily cyclosporine dose. Evidence of significant CE at the time of the biopsy included atheroemboli in the afferent arterioles, glomeruli, and large muscular arteries, with thrombosis and infarction of the renal cortex. This, combined with the lack of histopathologic features of cyclosporine nephrotoxicity, makes it unlikely that the allograft dysfunction was from cyclosporine alone. Furthermore, it is unlikely that cyclosporine therapy itself leads to CE.

Recent trends toward accepting older patients as both donors and recipients may increase the frequency of transplant-associated CE. Despite these trends, cholesterol emboli are still very rarely encountered in clinical transplantation. CE originating in the recipient would be expected to show features of a systemic disorder, whereas those originating in the donor may result in disease limited to the allograft, as was the case in our patient. In elderly donors with atherosclerotic vascular disease, atherosclerotic involvement of the renal vessels should be identified and care should be taken not to disrupt plaque during harvesting or transplantation. Large atheroma or plaque may require donor or recipient endarterectomy before transplantation. On the basis of our experience, lowering the cyclosporine dose may alleviate the renal toxicity associated with CE.

CE is a common, but underdiagnosed condition that most frequently arises in patients with atherosclerotic disease as a complication of the performance of an invasive vascular procedure, angiography, or anticoagulation. Cholesterol emboli in renal transplant re-
Cholesterol Emboli In Renal Allografts

Recipients can arise from the manipulation of either donor or recipient vessels. As our patient demonstrates, corroborating signs and symptoms may be absent, even if carefully pursued, especially if donor vessels give rise to atheroemboli. Nonetheless, lessons learned from the presentation of cholesterol emboli in the usual nontransplant setting appear to be generally applicable to transplant recipients. Foremost among these is to maintain a low threshold for performing biopsy with early allograft dysfunction and to consider the occurrence of atheroemboli when either donor or recipient vessels demonstrate evidence of significant atherosclerotic deposits.

REFERENCES