Case Report

Cholesterol embolization and severe vascular rejection in a renal allograft recipient

Lutz Renders¹, Kerstin Amann², Harald Schoecklmann¹, Hendrik Lehnert³ and Christian Stefan Haas³

¹Department of Nephrology and Hypertension, University of Kiel, Germany, ²Department of Pathology, University of Erlangen-Nuernberg, Germany and ³Department of Medicine I, University of Luebeck, Germany

Correspondence and offprint requests to: Christian Stefan Haas; E-mail: cs_haas@yahoo.com

Abstract
Cholesterol embolization (CE) is a well-known cause of renal dysfunction, often leading to irreversible renal failure most often in elderly patients. However, because of its unspecific and subclinical appearance, CE is often misdiagnosed. As donors and recipients of increasing age or with prominent atherosclerotic disease are accepted for transplantation, CE in renal allografts may become more prevalent. Here, we report a case of a 31-year-old second renal allograft recipient with CE as a cause of early graft failure, followed by severe vascular rejection, eventually requiring nephrectomy.

Keywords: cholesterol emboli; renal transplantation; vascular rejection

Introduction
Renal cholesterol embolization (CE) has been described for many years as a well-known cause for renal dysfunction especially in elderly patients and as a rare but serious complication in kidney transplantation. Previous reports showed that atheroembolic events both from the kidney donor and the recipient usually result in impaired graft function and that CE must be considered as one reason for early renal allograft dysfunction.

Case report
A 31-year-old woman with end-stage renal failure and a history of severe vascular rejection in a first cadaveric renal transplant received a second allograft. The surgical procedure was uneventful with cold and warm ischaemia times being 10 h and 40 min, respectively. Ultrasound examination of the graft revealed homogeneous perfusion but lack of end-diastolic perfusion in the interlobular arteries. The kidney donor was a 55-year-old male who had died of a cerebrovascular insult. He had no history of renal disease with a creatinine level reported to be 0.6 mg/dL (53 μmol/L).

Due to primary graft dysfunction, a routine allograft biopsy was performed on Day 7, revealing mild signs of acute tubular necrosis (ATN) and prominent CE of the small arteries and arterioles. Clinically, the patient showed no other signs of CE, serum levels for C3 and C4 were normal and eosinophilia was absent. Immunosuppressive therapy was not changed. On Day 15, a second specimen was obtained, demonstrating even more prominent CE with obliterative proliferation of myofibroblasts and typical biconvex-shaped clefts in renal arterioles. In addition, ATN and signs of mild, non-aggressive interstitial-cellular rejection were present. On Day 27, a third allograft biopsy revealed similar histological features with progression to an aggressive interstitial-cellular rejection, resulting in high-dose methylprednisolone therapy. Another biopsy 10 days later showed distinct intimal myofibroblast proliferation and significant stenosis of small- and medium-sized arteries, inflammation and fibrinoid necrosis of vessel walls and mild interstitial lymphohistiocytic infiltration, suggesting severe vascular graft rejection. No biconvex-shaped clefts were seen at this time. Despite additional aggressive immunosuppressive therapy, renal transplant function could not be established. Eventually, the graft was surgically removed, immunosuppression was stopped and the patient was discharged 2 weeks later undergoing chronic haemodialysis treatment.

Histological examination of the explanted kidney (Figure 1) demonstrated multiple biconvex-shaped clefts in small arteries almost in all regions, pronounced stenosis of small, medium and large arteries with endothelial damage and obliterative intimal myofibroblast proliferation as well as blood extravasation and tubulointerstitial lymphocytes. C4d staining was not performed. The glomeruli appeared normal. The pathological diagnoses were massive CE and chronic vascular rejection.

Discussion
CE is a well-known problem particularly in elderly patients with diffuse atherosclerosis, in the majority of cases...
Transplant cholesterol embolization

following iatrogenic vascular manipulation [1]. The clinical presentation of CE can be quite variable and includes cyanosis and gangrenous lesions in extremities as the typical livido reticularis with intact peripheral pulses, acute visual deficits, abdominal pain due to mesenterial ischaemia or renal dysfunction [2]. Normally, renal dysfunction due to atheroemboli has an acute or subacute onset with gradual impairment of glomerular filtration rate.

Eosinophilia is seen in ~60–80% of renal CE [3], and hypocomplementaemia as well as eosinophilic leucocytes in the urine usually support the clinical suspicion of renal CE. Laboratory test results may be particularly important in the absence of recent vascular manipulation and no clinical signs of extrarenal manifestation [1,4]. In many cases, the definitive diagnosis can be established only on histopathological ground [5].

Histologic features of renal CE are initial occlusion of small arteries and arterioles with a perivascularr inflammatory reaction: polymorphnuclear and eosinophilic infiltrations around the affected vessels, followed by mononuclear cell inflammation and sometimes giant cells [4]. Typical findings in biopsy specimens include biconcave, needle-shaped clefs within the occluded vessels, being the result of dissolving cholesterol crystals during tissue fixation. These initial lesions emerge in intimal hyperplasia and perivascular fibrosis encouraging blood vessel occlusion. Due to ischaemic injuries, acute tubular necrosis may be observed early, while glomerular sclerosis and tubular atrophy are present in later stages of the disease. Arcuate and intralobular arteries are more commonly involved than glomeruli. Due to a patchy distribution, a kidney biopsy specimen may not always reveal the classic pathognomonic lesions or may demonstrate very different stages of the disease. The diagnostic sensitivity of a single renal biopsy is ~75% for CE, improving to 94% with a second biopsy specimen [1]. Data of further serial biopsies are not available.

The overall incidence of renal CE varies in the literature from 1 to 4% with only sparse data available in renal allografts [1]. A recent retrospective analysis of 1500 renal transplant recipients revealed only seven cases (0.47%) of renal allograft atheroemboli [6]. Some studies suggest that renal allograft CE originates both from the recipient and donor in equal shares, whereas donor-related CE has a poorer outcome with regard to graft function [6,7]. A recent clinicopathologic study in 12 patients showed that the probable source of CE was the recipient in 75% and donor in 25% [8].

In the present case, diagnostic findings of CE after renal transplantation were unexpected, since pre-transplant evaluation did not reveal any evidence for atherosclerotic disease, and no diagnostic angiographic procedure was reported. The probability of donor-originated CE is supported by the history of a cerebrovascular accident in the kidney donor. However, neither the kidney report nor the transplant surgeon mentioned atherosclerotic changes in the donor organ or vessels. Massive CE, as shown in the first biopsy, probably contributed to primary graft dysfunction in our patient. While CE may be associated with mild signs of ATN and minor interstitial cellular infiltration, ATN per se is a common reason for primary dysfunction of renal allografts. Doppler ultrasound results in our patient were consistent with both disease entities. Previous data suggest that immediate graft dysfunction following transplantation associated with CE has a poor outcome [9]. However, favourable outcomes following kidney transplantation have been described [10].

The findings in later biopsies as well as in the removed allograft were consistent not only with renal CE but also with additional severe vascular rejection. Both, CE and vascular rejection, share certain pathophysiological mechanisms such as endothelial damage and histopathological features as the myofibroblast proliferation leading to vascular narrowing. It is unclear whether there is a relationship between a preceding atheroembolic event and subsequent vascular rejection. We conclude that CE as a cause of primary graft
dysfunction might be underestimated in renal transplants because of its patchy nature and possible association with the presence of other histological findings.

Conflict of interest statement. None declared.

References


Received for publication: 11.10.09; Accepted in revised form: 13.10.09