Kidney Transplant Graftectomy by Severe Mixed-Type Rejection with Acute and Chronic Active Vascular Lesions at Entire Levels of the Renal Vasculature

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Keywords

Allograft rejection · Endarteritis · Transplant arteriopathy · Transplant graftectomy · Thrombotic microangiopathy

Abstract

Vascular lesions related to allograft rejection have a big impact on graft survival. As such, investigation of these lesions is important to understand the pathophysiology of rejection and its management. We report a case of kidney transplant graftectomy by severe mixed-type rejection with acute and chronic active vascular lesions caused by non-adherence to immunosuppressive treatment. The patient presented is a 29-year-old male who received a kidney transplantation in July 2011 (ABO compatible) from his father. He then did not come to the hospital for 3 months prior to his admission and also made his own decision to stop his medication regimen. On October 2013, the patient came to the hospital with dyspnea, nausea, and vomiting and had significant renal dysfunction (serum Cr 30.4 mg/dL, BUN 191 mg/dL). A kidney graft biopsy showed cortical necrosis with severe interstitial hemorrhage and thrombotic microangiopathy (TMA). Despite steroid pulse therapy, kidney graft function did not recover, and the patient underwent a subsequent graft resec-

tion. The resected kidney graft displayed various vascular lesions from the renal artery to the interlobular arteries and arterioles including endarteritis, TMA, fibrinoid necrosis, and transplant arteriopathy. This case shows the detailed pathological findings of the vascular lesions in the entire artery tree of kidney allograft, and the pathophysiology is discussed.

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Background

To improve graft survival after kidney transplantation, it is necessary to treat active rejection adequately based on the correct diagnosis. Kidney allograft biopsy remains the major tool for the diagnosis of allograft rejection. Allograft rejection is pathologically classified using Banff classification [1]. Under these criteria, the vascular lesion is the critical prognostic factor of kidney graft survival [2, 3]. Therefore, it is important to observe pathological changes of the arterioles and arteries in the kidney allograft.

Here, we report a case of kidney transplant graftectomy by severe mixed-type rejection with various vascular

Fig. 1. Biopsy specimen of a kidney graft on admission. **a** Diffuse and severe interstitial hemorrhage is shown (Masson, $\times 100$). **b** Glomerular vascular pole was occluded by thrombus and most of the capillaries appear congested (Masson, $\times 400$). **c** Interlobular artery occluded by mononuclear cells and foam cell infiltration (Masson, $\times 400$).

Fig. 2. Macroscopic finding of resected kidney graft. Weight: 270 g, Length: $125 \times 80 \times 50$ mm. Massive bleeding was identified in the kidney parenchyma.

lesions as a result of non-adherence to immunosuppressive treatment. Usual kidney biopsies only observe limited parts of the kidney artery or arterioles. However, this case allowed observation of various vascular lesions from the renal artery to the interlobular arteries and arterioles. We show the detailed pathological findings of these vascular lesions and discuss the pathophysiology.

Case Report

The patient presented is a 29-year-old male with ESRD and IgA nephropathy that was diagnosed in 1999. He was started on peritoneal dialysis in February 2011. In July 2011, he received a kidney transplantation (ABO compatible) from his father. Following surgery, immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and methylprednisolone was started. On June 2012, his serum Cr increased from 1.3 to 3 mg/dL, and he was diagnosed with acute T-cell-mediated rejection (TCMR; Banff ACR

Fig. 3. Histological findings of resected kidney graft. **a** Interlobular artery occluded by fibrin thrombus. Endothelial swelling and infiltration of inflammatory cells resulted in narrowing of the lumen of another artery (elastic Masson, $\times 100$). Segmental double contour of the glomerular basement membrane and intracapillary mononuclear cells were recognized (PAM, $\times 400$). **b** Transmurular arteritis with fibrinoid necrosis was seen in the arcuate artery. Intimal thickening without elastosis (neointima) with infiltration of

inflammatory cells was identified in the arcuate artery; transplant arteriopathy (elastic Masson, $\times 50$). **c** The lumen of the interlobular artery was narrowed by severe neointimal formation. The artery wall was partly destroyed by transmural arteritis (elastic Masson, $\times 50$). **d** The branch of renal artery showing intimal thickening without elastosis and focal destruction of intimal elastic lamina (elastic Masson, low-power field: 300 μm scale was inserted).

type IIA) via kidney graft biopsy. Post diagnosis, he was administered a two-course steroid pulse therapy and his serum Cr improved to 2.3 mg/dL. As of July 2013, he did not come to the hospital and stopped his medication regimen on his own. On October 4, 2013, he came to the emergency department with dyspnea and nausea and was admitted for investigation of exacerbation of graft function.

Following admission, hematological tests revealed a BUN level of 191 mg/dL and a Cr level of 30.4 mg/dL. On admission, he had pain and tenderness in the lower right abdomen and a CT scan revealed an enlarged transplanted kidney. On day 1 of admission, he was started on hemodialysis for uremia and pulse steroid ther-

apy, MMF, and Tacrolimus for organ rejection after stopping immunosuppressive medication.

On day 14 of admission, we performed a kidney graft biopsy and started steroid pulse therapy. The pathological diagnosis was cortical necrosis with severe interstitial hemorrhage, thrombotic microangiopathy (TMA), and moderate endarteritis as shown in Figure 1. C4d staining was positive in the residual peritubular capillary (PTC). Based on the pathological findings, we thought that kidney graft function could not be rescued. A graftectomy was performed on day 35 of admission because of persistent symptoms.

The weight of resected kidney graft increased to 270 g from 118 g. Massive bleeding was identified in the kidney parenchyma

Fig. 4. Immunohistochemical findings of resected kidney graft. **a** CD68-positive macrophages infiltrated the cv lesion of the interlobar artery ($\times 400$). **b** Massive CD68-positive macrophages aggregated

in the arcuate artery ($\times 400$). **c** CD68-positive macrophages infiltrated in the glomeruli ($\times 400$). **d** C4d was detected in PTC by immunohistochemical stain ($\times 200$). PTC, peritubular capillary.

(Fig. 2). Various pathological changes were observed in the removed kidney graft caused by allograft rejection in a widespread area (Fig. 3, 4). We also observed fibrin thrombi from the glomerular vascular pole to the interlobular artery as seen in the biopsy specimen. Additionally, glomeruli without thrombi showed severe transplant glomerulopathy with moderate transplant glomerulitis (Fig. 3a). Transmural arteritis with fibrinoid necrosis was seen in the larger arteries, but it was most prominent in the arcuate artery (Fig. 3b). On the other hand, severe transplant arteriopathy was remarkable in the arcuate and interlobar arteries (Fig. 3c). It almost reached the branch of the main renal artery (Fig. 3d).

Additionally, glomeruli without thrombi showed severe transplant glomerulopathy with moderate transplant glomerulitis. Transmural arteritis with fibrinoid necrosis was seen in the larger arteries, but it was most prominent in the arcuate artery. On the other hand, severe transplant arteriopathy was remarkable in the arcuate and interlobar arteries. It almost reached the branch of the

main renal artery. In some of these vascular lesions, massive CD68-positive macrophage infiltration was prominently identified (Fig. 4a, b). Macrophages were also infiltrated in glomeruli (Fig. 4c). Further, the tubulo-interstitial area widely showed necrosis or edema with infiltrative cells. Thus, we could not evaluate the degree of tubulitis. The residual PTC showed mild peritubular capillaritis. Positive C4d staining was observed in PTC (Fig. 4d). On day 65 of admission, he was discharged with no complications.

Discussion

Until the revision of the Banff 2013 classification, vascular lesions (with the exception of fibrinoid necrosis [v3]) have mainly been considered as pathological chang-

es resulting from TCMR [4]. However, after the 2013 Banff classification revision, endarteritis (v1 and v2) was also included in the antibody-mediated rejection (AMR) pathological diagnostic criteria [5]. Therefore, it is difficult to distinguish TCMR from AMR based on the type of endarteritis, as was done previously before the revision. Regardless of a diagnosis with AMR or TCMR, a case with endarteritis has a worse graft survival [2, 3].

Regarding the TMA lesion, TMA in a kidney allograft has various causes, including CNI toxicity, malignant hypertension, recurrent HUS/TTP, and allograft rejection [6]. Although the typical vascular lesion of AMR is fibrinoid necrosis or transmural endarteritis [7], TMA is also occasionally seen in severe AMR. The prevalence of TMA in kidney allografts was reported to be 4–46% of AMR cases [8]. TMA with positive C4d staining in PTC highly indicates graft loss in AMR [9].

Given the above, the presence of these acute/active vascular lesions is a noteworthy finding of allograft rejection. In the present case, we were not able to distinguish clearly which type of rejection contributed to the cause of the acute/active vascular lesions related to allograft rejection. The v2 lesion, TMA, and fibrinoid necrosis shown in this case could be explained by AMR. Presence of microvascular injury (glomerulitis and peritubular capillaritis) concurrently with positive C4d staining in PTC also indicates that factors of AMR are closely involved in the origin of these active lesions. However, considering the clinical episode of severe non-adherence, AMR and TCMR might be pathophysiological factors.

Moreover, severe transplant arteriopathy (cv2~3) was also seen in this case. Most cases of transplant arteriopathy are related to preceding endarteritis by cell-mediated rejection [10]. The episode of ACR type IIA that occurred in the previous year may have been the leading cause of the lesion. The infiltration of CD68-positive macrophages in the cv lesion was also remarkable. Activated macrophages play an important role in vascular remodeling of chronic rejection and can progress to neointima, which is the pathologic feature of transplant arteriopathy [11]. As such, infiltrating macrophages might be associated with the formation of the cv lesion in this case.

It is known that AMR is one of the major causes of graft failure [12]. In fact, previous reports have revealed that production of de novo donor-specific antibody (DSA) due to non-adherence causes AMR [12]. It is not obvious when this patient stopped immunosuppressive medications. However, the presence of chronic lesions like the severe cv lesion and transplant glomerulopathy indicate that the patient was long-term non-adherent.

Long-term drug discontinuation might affect the appearance of de novo DSA. We did not perform the examination to detect DSA; however, C4d deposition in PTC may indicate the presence of DSA. Recently, Hill et al. [13] reported that cv lesions progressed rapidly in patients with DSA. They proposed the concept of accelerated arteriosclerosis. This may have partially affected the progression of cv lesion formation in this case.

Clarifying the degree and extent of these vascular lesions is important for treating allograft rejection and predicting the prognosis of graft survival. However, it is often unclear as to which size of arteries such vascular lesions actually extend to. In an experimental model of acute and chronic vascular rejection, endarteritis and transplant arteriopathy were seen in the entire arterial tree with different degrees [14], coinciding with this case. When severe vascular lesions were observed in the kidney biopsy specimens, the likelihood of vascular lesions reaching the larger size arteries was considered.

In conclusion, we presented a case of kidney transplant graftectomy by severe mixed-type rejection with various vascular lesions. We should observe the pathological features of severe vascular lesions in detail to recognize the pathophysiology and determine adequate treatment. Moreover, we should consider the possibility that vascular lesions could reach the larger renal artery and attention should be paid to acute deterioration of the kidney graft function.

Statement of Ethics

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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