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Case report

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Histological changes of a kidney in a recipient who received an allograft from a patient with Fabry disease

Running title: Renal histological changes in a transplant patient receiving an allograft from a Fabry patient

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Case report

A 61-year-old man was referred to our hospital to undergo kidney transplantation (KT). He had been receiving dialysis therapy for the past 5 years. Although the cause of his end-stage kidney disease (ESKD) was not clearly identified, it was suspected to be glomerulonephritis based on the clinical course. He had hypertension and a history of myocardial infarction five years ago. Thus, he was admitted to our hospital for a detailed investigation before KT.

He and his wife were investigated to confirm whether they were an appropriate kidney transplant recipient and donor. They had no family history of kidney disease, cerebrovascular disease, or cardiovascular disease. No significant abnormalities were detected by detailed examinations, including the electrocardiogram, echocardiography, and laboratory tests. Her serum creatinine levels were 0.59 mg/dL. Urinalysis revealed no hematuria, and her 24-hour urinary protein excretion was within normal limits (78.4 mg/day). Taken together, we determined that she was an appropriate donor.

Thus, after a detailed investigation of both the recipient and a donor, KT was successfully performed. During the operation, a 1-hour kidney biopsy after reperfusion was also performed. Based on the histological findings, the donor was suspected to have FD. She had no findings typical of FD and normal α -galactosidase A activity of her white

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3 blood cells (74.8 nmol/mg/protein/hr; normal range: 49.8-119.4 nmol/mg/protein/hr)
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6 and dried blood spots (8.3 U/mL; normal range: 3.6-17.6 U/mL), and normal plasma lyso-
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9 Gb3 level (0.4 ng/mL; normal range: 0-2.0 ng/mL). The results of genetic analysis showed
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12 an α -galactosidase A mutation: guanine of the 1,124th base from the ATG of exon 1 was
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15 changed to a mixture of guanine and adenine. Taken together, we determined that a
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19 ESKD patient without FD received a kidney allograft from a patient with FD.
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25 Discussion

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28 Fabry disease (FD) is an X-linked inherited disorder of α -galactosidase A activity that
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31 results in the progressive accumulation of globotriaosylceramide (Gb3) within the
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34 lysosomes of various cells and tissues [1, 2]. Because of Gb3 accumulation, various
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37 organs, particularly the kidney, heart, and brain, are damaged, which results in various
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40 clinical problems. In case of patients with organ failure, if possible, organ transplantation
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43 is performed when possible. Although some patients with FD have possibilities to
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46 receive KT, some kidney transplant patients whose etiology has been unknown have
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49 been found to have FD after KT. There have been only several previous reports of
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52 patients without FD receiving transplanted kidneys from Fabry donors [3]. However,
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57 most of these cases were deceased-donor KTs. Living donors with FD rarely donate their
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3 kidneys to their relatives because living donors undergo a detailed examination before
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6 KT, and inappropriate persons are excluded from being donors.
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10 Identifying the etiology of ESKD is very important in KT because the recurrence of
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12 primary glomerulonephritis can be encountered during the post-transplant period [4]. If
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15 we can determine the presence of such diseases before KT, we can prepare for
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18 treatment against such diseases and prevent their recurrence. Furthermore, if patients
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21 have inherited diseases, we must assess our donor candidates more carefully because
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24 there is a possibility that they may have the same diseases. Generally speaking, it is very
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27 crucial to examine donors in great detail before KT, particularly for kidney disease,
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30 cardiovascular disease, diabetes mellitus, and hypertension, which can influence kidney
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33 function after KT. In the present case, we also performed detailed examinations,
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36 including electrocardiography, echocardiography, computed tomography, and 24-hour
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39 urinalysis, etc., before KT and these examinations all had completely normal results.
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42 However, the histological findings of 1-hour kidney biopsy after reperfusion from the
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45 Periodic acid-Schiff staining and Masson-trichrome staining revealed 11 glomeruli, 5 of
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48 which had fine cytoplasmic vacuolation of several podocytes. There were no fine
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51 vacuolar changes in tubular epithelial cells and vascular endothelial cells. Electron
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54 microscopic findings also revealed laminated high electron-dense and osmiophilic
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3 deposits, “zebra body”, in podocytes (Figure 1a-c). An immunofluorescence study using
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6 anti-Gb3 antibodies revealed a positive area on the glomeruli (Figure 1d). Interstitial
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9 fibrosis and tubular atrophy were not observed. There were no Gb3-positive cells in
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12 renal tubules and arteries. Arteriosclerosis of renal interlobular arteries and arteriolar
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15 hyalinosis were not observed. Although we couldn’t determine the presence of FD prior
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18 to KT, finally, she was diagnosed as FD. It made the diagnosis before KT difficult that the
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21 donor was female and her genetic mutation was a late-onset type [5]. There are several
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24 reports in which donors were diagnosed with FD by a graft biopsy after KT [3]. Thus, we
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27 must consider the possibility that a donor may have FD and pay great attention to the
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30 pre-transplant donor survey.
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35 The most valuable information in this case is the sequential evaluation of a
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38 transplanted kidney histology over five years. We always perform a protocol kidney
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41 biopsy after KT. Therefore, the present case received the kidney biopsies at one hour,
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44 three months and one, three, and five years. The number of all glomeruli and those with
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47 Gb3 accumulations was counted, and the percentage of glomeruli with Gb3
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50 accumulations was calculated. As shown in Table 1, the results of this analysis showed
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53 that Gb3 accumulation was gradually decreased after KT. Few reports have evaluated
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56 renal histological change in a recipient who received a kidney from a donor with FD, and
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3 this is the first case where a detailed and repeated histological evaluation of a
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6 transplanted kidney were performed. Aasebø W et al. reported that Gb-3 accumulation
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9 in transplanted kidneys remained unchanged even though they had been exposed to
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12 normal levels of circulating α -galactosidase A for 3 and 12 years [3]. Furthermore, the
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15 kidney function of these two cases remarkably worsened, which may not have been a
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18 result of FD. Conversely, in the present case, the accumulation of Gb3 in glomerular cells
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21 has gradually decreased year after year. The donor has received enzyme replacement
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24 therapy once a month after KT. Currently, both the recipient and donor have maintained
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27 preserved kidney function and normal findings on urinalysis.
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32 Here, we reported that the first case of a kidney transplant recipient who showed a
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35 gradual decrease in intrarenal accumulation of Gb3 after KT. Gb3 accumulation in a
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38 kidney allograft may gradually disappear when the kidney of a patient with FD is
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41 transplanted into a patient without FD.
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Table 1 Change in intrarenal accumulation of Gb3

Timing of biopsy after kidney transplantation	Total number of glomeruli	Number of glomeruli with Gb3 accumulation	Percentage of glomeruli with Gb3 accumulation (%)
1 hour	11	5	45.5
3 months	18	9	50.0
1 year	20	6	30.0
3 years	39	6	15.4
5 years	19	4	21.1

Gb3, globotriaosylceramide.

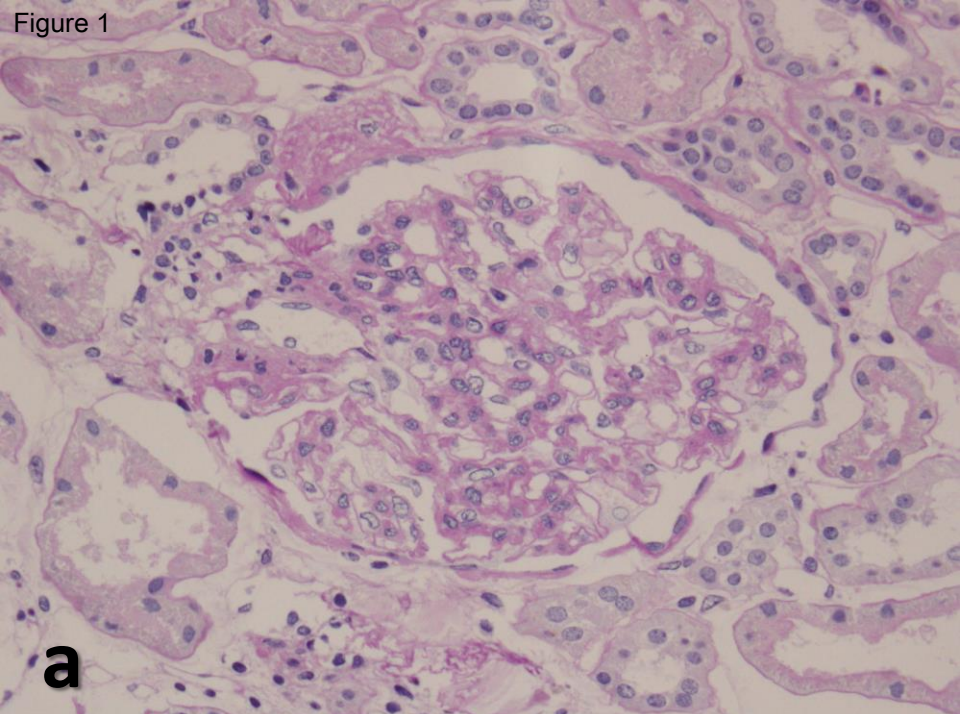
Figure Legends

Figure 1. Representative renal histology

- a. Periodic acid-Schiff stain (PAS)
- b. Masson-trichrome (MT) staining
- c. Electron microscopic (EM) finding
- d. Immunofluorescence (IF)

Light microscopy showed vacuolation of several podocytes (Figure 1a, PAS, original magnification $\times 400$; b, MT, original magnification $\times 400$). Electron microscopy revealed high electron-dense and osmiophilic deposits in podocytes (c, EM, $\times 6000$). An immunofluorescence study with anti-Gb3 antibodies revealed a positive area on glomeruli (d, IF, original magnification $\times 400$).

Figure 1



[Click here to access/download;Figure;FD in KT \(Figure 1\).pptx](#)

