

Renal Lymphangiectasia, a Rare Complication After Kidney Transplantation



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INTRODUCTION

Surgical complications are an important issue after kidney transplantation. Lymphatic disorders are frequent, especially lymphocele, lymphorrhea, or lymphorrhagia that most often occur in the first months after transplantation and affect up to 40% of kidney transplant recipients.¹ Besides the surgical risk factors, other contributors have been increasingly recognized such as obesity, certain immunosuppressive drugs, and acute rejection episodes.² The diagnosis has been improved along with the development of cutting-edge imaging examinations and the wide use of magnetic resonance imaging (MRI).³ Up to 15% of lymphoceles require specific treatment, the most efficient option of which being laparoscopic fenestration, given the high risk of recurrence after simple percutaneous drainage.⁴

Renal lymphangiectasia, also known as renal lymphangiomatosis,^{5–7} is an uncommon complication after kidney transplantation. This rare condition, most often benign, is characterized by ectasia of peripelvic, perirenal, and/or intrarenal lymphatic vessels. Few descriptions have been reported in the literature, exceptionally after kidney transplantation,⁷ and there is currently only sparse data on the clinical presentation, pathophysiology, and therapeutic options in kidney transplant recipients.

We present here two cases of kidney transplant lymphangiectasia revealed by persistent ascites and atypical abdominal pain, without kidney graft dysfunction.

CASE 1

A 34-year-old man was referred to our department for refractory ascites 10 years after first kidney transplantation for end-stage kidney disease secondary to idiopathic focal and segmental glomerulosclerosis. He had experienced a biopsy-proven acute subclinical humoral rejection revealed by the occurrence of *de novo* donor-specific antigens 4 years after transplantation. Rejection was treated with corticosteroids, intravenous immunoglobulins, and immunoadsorption (10 sessions). The serum creatinine level remained stable at 0.9 mg/dl, as well as urinary albumin-to-creatinine ratio at 50 mg/g. He was then maintained on a combination of tacrolimus, mofetil mycophenolate, and steroids. Ascites gradually appeared 8 years after transplantation, leading to an increasing discomfort. There was no associated sign of peripheral edema. Cardiac function was normal and there was no nephrotic syndrome. Ascites was transudative, non-chylous, and without evidence for infectious or malignant disease. Abdominal MRI did not show liver structural abnormality and positron emission tomography scan did not find any evidence for cancer or lymphomatous disease. There was also no sign of retroperitoneal lymph nodes or fibrosis. A liver biopsy was also performed and did not reveal any significant abnormality. Given the hypothesis of mycophenolate-induced regenerative nodular hyperplasia, which may not be detected on biopsy findings, a conversion to mammalian target of rapamycin (mTOR) inhibitor (mTORi) was performed. Magnetic resonance urography (MR-urography) showed significant nephromegaly (13.7 cm, 603 cc) with multiple

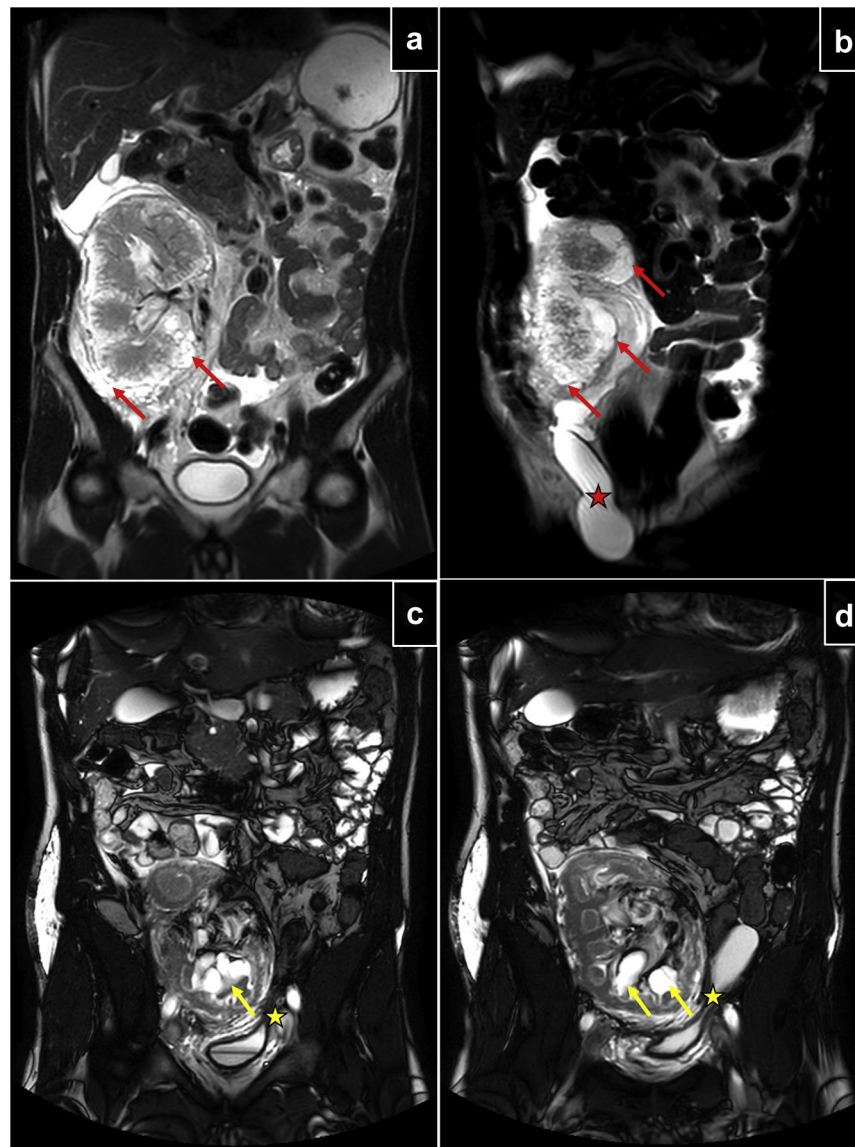


Figure 1. MR-urography findings regarding patient 1 and patient 2. (a,b) Patient 1. (c,d) Patient 2. Both examinations revealed major nephromegaly with multiple plurilobular fluid collections of different morphological patterns: peripheral development at the upper and lower poles of the graft (patient 1: red arrows); parapyelic, juxtacapsular, and perihilar (patient 2: yellow arrows). The magnetic resonance urographies also showed local mechanical complications of kidney graft lymphangiectasia: large inguinoscrotal hydrocele (red star, **b**) and bladder compression (yellow stars, **c** and **d**).

peripheral plurilobular fluid collections at the upper and lower poles of the kidney graft as well as extensive ascites responsible for inguinoscrotal hydrocele (Figures 1a and 1b). A kidney graft biopsy was performed and revealed chronic active humoral rejection and significant interstitial edema, but no argument for post-transplantation lymphoproliferative disorder. Retrospectively, the transplanted kidney had normal appearance at the time of procurement with no cyst detected. However, 4 years before the recent episode of ascites (6 years after transplantation), an ultrasound scan was performed because of intermittent pain in the graft area: its size had already increased (13 cm) and a significant amount of fluid (4-mm-thick) outlined the graft, which argued for perirenal lymphangiectasia (Figure 2). This led us conclude to

cortical and perirenal lymphangiomatosis. One year after mTORi conversion, the patient experienced better control of ascites and pain relief, but the kidney graft volume was still moderately increasing (14.3 cm, 654 cc). Regarding graft function, the serum creatinine level remained stable at 1.1 mg/dl. A prosthetic parietal surgery under the Lichtenstein procedure was also proposed for the treatment of inguinoscrotal hydrocele, but the patient preferred to decline the proposition.

CASE 2

A 35-year-old man was referred to our department for chronic pelvic pain associated with urinary symptoms 8 years after first kidney transplantation for end-stage

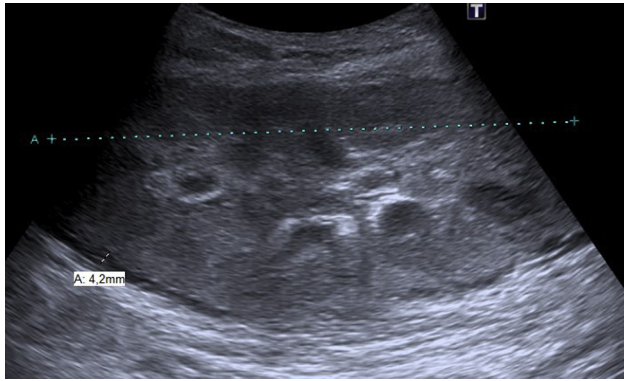


Figure 2. Renal ultrasound. Significant nephromegaly is shown (13 cm) and a thin perirenal hypoechoic layer (4.2 mm), suggestive of peripyelic cysts and lymphangiectasia.

kidney disease secondary to typical childhood hemolytic and uremic syndrome. Five years after transplantation, he experienced a biopsy-proven subclinical acute humoral rejection (graft biopsy performed because of *de novo* donor-specific antigen). Therefore, he underwent a treatment combining corticosteroids, intravenous immunoglobulins, and six plasma exchange sessions. The renal serum creatinine level remained stable at 1.1 mg/dl as well as the urinary albumin-to-creatinine ratio at 32 mg/g. Maintenance immunosuppressive therapy relied on a combination of tacrolimus, mofetil mycophenolate, and steroids. Given the recent symptoms, an abdominal ultrasound was performed and found a significant nephromegaly (16 cm), associated to normal pyelocaliceal cavities, multiple peripyelic cysts, perihepatic, and perisplenic ascites. On physical examination, there was no sign of peripheral edema. The graft vein flow was also considered turbulent. An abdominal MRI was performed and did not find any evidence for peritoneal lymphomatous disease, nor pathological retroperitoneal lymph nodes or fibrosis. Ilio-vena cava venography ruled out any graft venous stenosis. Finally, MR-urography and MR-angiography of the kidney graft confirmed major nephromegaly ($8.5 \times 12.5 \times 17$ cm, 729 cc), multiple parapyelic cysts, pericapsular lymphangiectasias, and edematous infiltration of perirenal fat, the whole being responsible for bladder compression. Retrospectively, at the time of transplantation, the kidney graft measured 11.3 cm, without any cyst. No peripyelic cyst had been described at the time of transplantation, nor on another ultrasound performed 2 years after. When kidney graft biopsy was performed to diagnose subclinical acute humoral rejection 3 years after transplantation, kidney size was 13.5 cm. On the basis of imaging outcome (especially MR-urography), the diagnosis of kidney graft lymphangiomatosis with a specific perihilar development was made (Figures 1c

and 1d) and mofetil mycophenolate was switched to mTORi. Although ascites was better controlled, graft size significantly increased 6 months later ($8.5 \times 13.5 \times 18$ cm, 910 cc). mTORi was then withdrawn and mofetil mycophenolate restarted. Three months later, the kidney graft volume partly decreased (17 cm, 770 cc) but ascites reappeared.

DISCUSSION

We describe two cases of kidney graft lymphangiectasia responsible for persistent ascites and symptomatic nephromegaly revealed by atypical chronic pelvic pain and local mechanical complications: inguinoscrotal hydrocele (patient 1) and bladder compression (patient 2).

Renal lymphangiectasia is an extremely rare pathology. Only 50 cases have been reported, almost exclusively in native kidneys.⁷ Its pathophysiology remains unclear. A defective connection between kidney lymphatic vessels and large retroperitoneal lymphatics has been hypothesized. This would lead to lymphatic fluid accumulation and induce hyperpressure and ectasia of the lymphatic vessels, contributing to the formation of intra- and perinephric collections. Anatomically, lymphatic vessels are particularly abundant in the cortex, unlike the medulla.^{8,9} The development of lymphatic vessels is controlled by pro-lymphangiogenic factors (vascular endothelial growth factors [VEGF] C and D) binding to VEGF3 receptors. To the best of our knowledge, only one previous report has described lymphangiectasia in a kidney graft.⁷ The mechanical hypothesis cannot fully explain the pathophysiology of the disease because anastomosis of the lymphatic vessels is never performed during kidney transplantation. However, another cause of mechanical lymphatic obstruction should always be excluded: in the case of patient 2, for example, MR-angiography was also performed given the initial hypothesis of vein kinking. A genetic predisposition has been suggested but the outcome of the paired kidneys is unknown in both our cases. Nevertheless, the morphology of these kidney transplants was normal at the time of procurement. Finally, the hypothesis of lymphatic overproduction and enhanced lymphangiogenesis due to pro-inflammatory events, such as acute rejection or acute kidney injury, appears to be the most attractive, these situations precisely promoting VEGFC/VEGFD secretion by cortical and medullary tubular epithelial cells.^{1,8,9} Because of the steady progress in the management of kidney graft rejection in the past few years, this may also explain why this pathological entity has only been recently

described for the first time in kidney transplant recipients.

Considering atypical ascites and nephromegaly, we were primarily concerned about the diagnosis of post-transplantation lymphoproliferative disorder. Our two patients had been transplanted for almost 10 years and both grafts were provided by young donors (23 and 28 years old, respectively). Interestingly, in the two cases previously described by Dawidek *et al.*,⁷ the donors were pediatric. Another common characteristic between our cases and those previously described is the past history of acute rejection. In patient 2, active lesions associated to chronic humoral rejection were still present at the time of diagnosis. Thus, as mentioned above, a chronic inflammation state might have promoted lymphorrhea. In contrast with renal lymphangiectasia in native kidneys, which is often associated to kidney dysfunction, graft function was well preserved in these transplant patients despite their previous rejection episodes.⁷ One can hypothesize that high VEGFC might play a protective role against renal fibrosis.⁸

These two cases show different anatomical presentation patterns, from cortical to perihilar involvements, and highlight how the diagnostic approach may be particularly challenging.^{3,5,6} Previous imaging examinations revealed a progressive kidney graft enlargement in both patients and kidney graft ultrasound had already suggested the diagnosis of lymphangiectasia 3 years earlier in patient 1. In both patients, before the occurrence of clinical symptoms, radiologists already described the presence of a thin perirenal hypoechoic layer or peripyloric cysts, suggesting intra- or perirenal lymphangiectasia. Renal lymphangiectasia is thus an exclusion diagnosis which relies on the combined findings of sequential imaging examinations (ultrasound, computed tomography scan, MRI).⁶ Ascites seems to be an important diagnostic criterion shared by all the described cases until now. It is also possible that, in the absence of ascites, the diagnosis may never be made given the difficult diagnostic approach and the imaging abnormalities not easily noticed at the early stage of the disease.

As pathophysiology is still poorly understood, there is currently no effective treatment, and strategies used for the management of lymphoceles have been applied.^{1,7} In the case series of Dawidek *et al.*,⁷ despite several invasive procedures (percutaneous drainage, marsupialization, renal capsule sclerosing, and sealing), the outcome ultimately resulted in refractory ascites leading to transplantectomy for both patients. The use of lymphangiography and embolization has been mentioned, but this procedure would have been particularly risky and noncontributory given the practical difficulty of catheterizing the graft lymphatic vessels, which are not anastomosed to the recipient's

Table 1. Teaching points

Renal lymphangiectasia is a very rare disease that may exceptionally occur after kidney transplantation.
This exclusion diagnosis should be suspected in case of multiple perirenal and/or peripyloric cysts, responsible for progressive nephromegaly and atypical ascites.
The challenging diagnostic assessment requires sequential imaging and multidisciplinary approach.
The prognosis is mostly driven by local mechanical complications and alteration of quality of life.
There is no specific treatment and nephrectomy may be justified in case of poor outcome.

drainage system. The question of nephrostomy and marsupialization was also raised but not retained given its low expected yield: indeed, unlike large classical lymphocele, kidney lymphangiectasia are made of a complex network of multiple small cystic collections developed around or even within renal parenchyma. Because of the unsuccessful experience reported by Dawidek *et al.*⁷ with these treatment options, and the substantial risk of graft loss while renal function was still preserved in our recipients, we did not opt for any invasive management after collegial discussion. As mTORis are widely used in kidney transplantation and could inhibit lymphangiogenesis, which may explain their significant association with increased risk of lymphocele,^{1,9} we proposed a conversion from mofetil mycophenolate to everolimus. In both patients we observed a better control of ascites but no impact on graft enlargement, which suggests a limiting effect on lymphangiogenesis and/or lymphatic drainage without affecting lymphatic overproduction. After mTORi discontinuation in patient 2, the graft volume decreased but ascites rapidly reappeared. Moreover, because of the preserved renal function and the absence of peripheral edematous syndrome in both our patients, we did not prescribe any diuretic treatment. It is therefore unlikely that the control of ascites would be related to any blood volume variation. However, given the lack of mTORi effect on the course of lymphangiectasia in the study of Dawidek *et al.*,⁷ any conclusion regarding this treatment option should be drawn with caution. Finally, in the absence of effective therapy, transplantectomy might be discussed according to the deleterious impact of lymphangiectasia on quality of life.

Lymphangiectasia is an exceptional cause of nephromegaly and atypical ascites in kidney transplant recipients.⁷ Its prognosis depends on local mechanical complications. The two present cases, and the previously reported ones, share several common characteristics: late onset after transplantation (5 to 10 years after transplantation), younger recipients and donors, and a history of acute rejection but preserved long-term graft function. Imaging shows very heterogeneous anatomical presentations. The outcome after mTORi introduction and discontinuation brings new insights on

pathophysiology of lymphangiectasia. A multidisciplinary diagnostic approach, based on sequential imaging, can help to avoid misdiagnosis as well as numerous invasive and expensive examinations (Table 1).

AUTHOR CONTRIBUTIONS

Conceptualization: AH, PP, MM, SB, MH, AL. Data acquisition: AH, PP, MM, MH, AL. Manuscript drafting: AH, AL, PP, MH. Critical revision: AH, PP, MM, SB, MH, AL. Manuscript approval: all the authors.

DISCLOSURES

The authors declare that they have no conflict of interest.

PATIENT CONSENT

Both patients of these case reports have given their consent for publication.

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