

Everolimus-induced Lymphedema in a Renal Transplant Recipient: A Case Report

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Abstract

The mammalian target of rapamycin inhibitors is commonly preferred for solid organs for transplantation. Although these drugs have various adverse effects, sirolimus-related lymphedema has been rarely reported.

We report a case of lymphedema related to everolimus after a kidney transplant. A 60-year-old woman successfully received a deceased-donor kidney. Everolimus was added to the treatment in postoperative month 3 owing to other immunosuppressive drugs' adverse effects. Edema occurred first on her feet in the first year after the transplant. During 3 months' follow-up, with no immunosuppressive adjustment, the edema progressed. Diagnosis of lymphedema was established. Several weeks after discontinuing everolimus, the patient's lymphedema began to resolve itself and completely disappeared in 3 months. The mammalian target of rapamycin inhibitors rarely causes lymphedema by inhibiting different subtypes of vascular endothelial growth factors, which results in impaired lymphangiogenesis. While there are few reports about sirolimus-related lymphedema, this case represents the first everolimus-related case of lymphedema. Further studies are warranted to explain the underlying mechanisms.

Key words: *Edema, Immunosuppression, Kidney transplant, mTOR inhibitors, Complication*

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Introduction

The mammalian target of rapamycin (mTOR) is an intracellular convergence point for numerous cellular signaling pathways that regulate several biologic processes that are essential for cell proliferation, angiogenesis, and cell metabolism. Sirolimus and everolimus are both macrolides that inhibit the mTOR pathway, which has proven benefits in the areas of transplant, oncology, and cardiology. Adverse events related to these drugs include poor wound healing, delayed graft function, skin lesions, anemia, proteinuria, interstitial pneumonitis, gonadal suppression, hyperlipidemia, and increased incidence of lymphocele.¹

A less-common form of edema is lymphedema, which causes an abnormality in the lymphatic system. The most-common cause is interruption of the axillary lymphatic system by surgery and/or radiation therapy in women with breast cancer. Spontaneous formation of lymphedema has been seen with sirolimus-based immunosuppression in renal transplant recipients.²⁻⁵ We report the first recipient who developed lymphedema 8 months after starting everolimus treatment.

Case Report

A 60-year-old woman with end-stage renal disease owing to polycystic kidney disease, received a deceased-donor kidney transplant in March 2007 after 3 years of peritoneal dialysis. The kidney was successfully transplanted to the left iliac vessels. The immunosuppressive regimen consisted of basiliximab, tacrolimus, mycophenolate mofetil, and steroids. One week after transplant, mycophenolate mofetil was withdrawn because of leucopenia and thrombocytopenia. The patient was discharged with a serum creatinine level of 106 mmol/L (1.2 mg/dL).

In postoperative month 3, everolimus was added to the treatment regimen. The everolimus dosage (0.5 to 1 mg/d) was adjusted to provide trough levels greater than 3 ng/mL. Tacrolimus was stopped because of hyperglycemia during postoperative month 9, and her serum glucose levels returned to normal. Mycophenolate mofetil was restarted. Edema was noticed on her feet during a routine transplant outpatient clinic visit in the first year of transplant. Abdominopelvic ultrasound and computed tomography showed no abdominal or pelvic masses except multiple liver cysts. An esophago-gastro-duodenoscopy and a biopsy were done because of wall thickening, from the second to the fourth part of the duodenum on abdominal computed tomography. Endoscopic diagnoses were gastric polyps, atrophic gastritis, and duodenitis. Pathological diagnosis was compatible with chronic atrophic gastritis. A colonoscopy, mammography, and bone scintigraphy indicated no signs of malignancy. A bilateral lower extremity Doppler ultrasound showed no signs of deep vein thrombosis or reflux.

The patient was followed for 3 months with no adjustment in the immunosuppressive regimen because the edema that started in her feet, progressed to the upper extremities and left breast. A lymphoscintigraphy scan revealed lymphedema in her left upper and lower extremities. No infectious agents were found in her blood or urine. The results of autoantibody and *cytomegalovirus* tests were negative. Everolimus was discontinued, and cyclosporine was added to the treatment. The patient's edema started to resolve within several weeks after we stopped giving her everolimus, and lymphedema completely disappeared within 3 months. The patient's graft kidney is working properly at the current time with a serum creatinine level between 88.4 and 123.7 mmol/L with no signs of edema.

Discussion

Lymphedema may be primary (congenital lymphatic abnormality) or secondary. Secondary (acquired) lymphedema is frequently related to cancer treatment. Other causes of secondary lymphedema include obstruction by tumor, infection (filariasis), recurrent cellulitis, and connective tissue disease. In our case, we excluded other secondary causes of

lymphedema, and everolimus-related lymphedema was considered. An immunosuppressive agent, sirolimus, was a rare cause of lymphedema.

Al-Otaibi and associates³ reported localized lymphedema in varying severity in 4 renal transplant recipients under different duration of sirolimus therapy (ranging from 7 months to > 2 years). Lymphedema, with or without ascites, pleural, and pericardial effusions have been reportedly improved by dosage lowering or discontinuing sirolimus in several renal transplant recipients.^{2, 5} Secondary lymphedema typically involves a single limb, while involvement that is more widespread may be seen in primary lymphedema. In our case, lymphedema began at the feet at the fifth month of everolimus therapy, and progressed to left upper limb and left breast within 3 months. No effusions were demonstrated with imaging methods. If imaging is performed to distinguish lymphedema from nonlymphatic causes of edema, lymphoscintigraphy is the preferred test. Rico and associates⁴ drew attention to subclinical rejection with lymphedema in a recipient with lower limb lymphedema owing to sirolimus, although the renal functions of our case were stable during lymphedema.

We did not find any case reports in the literature regarding everolimus-related lymphedema. Fuchs and associates⁶ reported 6 heart transplant cases (5 of 6 patients, lingual angioedema disappeared with antiallergic treatment alone, and 1 required discontinuation of therapy) with lingual angioedema; symptoms occurred within 2 to 41 days after initiation of everolimus therapy. The underlying mechanism of lymphedema has been explained by the combination of the lymphatic disruption secondary to the surgical procedures and increased vascular permeability and vasodilatation caused by sirolimus. Sirolimus-related lymphedema is not dependent on its cumulative dosage and exposure duration.³

It has been reported in different experimental cancer models that sirolimus exhibits a strong tumor-specific antivasular effect and reduced lymphatic metastases by inhibiting vascular endothelial growth factor (VEGF)-A production and reducing responsiveness of vascular endothelial cells to VEGF-A.^{7, 8} Lymphatic endothelium expresses VEGF receptor-3 (VEGFR-3), which is activated after binding to VEGF-C, and VEGF-D plays an important role in lymphangiogenesis. Sirolimus interferes with

the intracellular pathway activation of lymphatic endothelial cells by VEGF-C. Interestingly, the gene that encodes VEGFR-3 (FLT4) is defective in most families with congenital hereditary lymphedema.⁹ Impaired lymphangiogenesis and lymphedema is observed in soluble VEGFR-3 (VEGF signaling inhibitor) expressing transgenic mice.¹⁰ Missense mutations of VEGFR-3 prevent normal lymphatic growth in humans.⁹ A potential antilymphangiogenic activity of the mTOR inhibitors could be well rationalized by the lymphatic complications observed in renal transplant recipients.

Huber and associates¹¹ hypothesized that sirolimus decreases regenerative and neoplastic lymphangiogenesis by inhibiting lymphatic endothelial cells. In rapamycin-treated animals, the antilymphangiogenic effect during tissue regeneration occurs with prolonged lymphedema, emphasizing the clinical relevance of this effect of the mTOR inhibition in renal transplant recipients. Furthermore, the present case indicates that everolimus may have an antilymphangiogenic activity. In case of lymphedema, the mTOR inhibitors should be changed immediately after secondary causes were eliminated.

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