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Lymphedema of the Transplanted Kidney and Abdominal Wall with Ipsilateral Pleural Effusion Following Kidney Biopsy in a Patient Treated with Sirolimus: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 32
Final Diagnosis: Sirolimus induced congestion of kidney and overlying abdominal wall
Symptoms: Abdominal pain • abdominal swelling • dyspnea
Medication: —
Clinical Procedure: Improvement of symptoms with drug withdrawal
Specialty: Nephrology

Objective: Adverse events of drug therapy

Background: Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor, which is used in immunosuppressive treatment regimens in organ transplant recipients. Although mTOR inhibitors are well tolerated, their adverse effects have been reported. Sirolimus treatment in transplant recipients has been reported to be associated with lymphedema of the skin and subcutaneous tissues, and with pleural effusion, but edema of internal organs and organomegaly have not been previously reported. A case is presented lymphedema of the transplanted kidney and abdominal wall with ipsilateral pleural effusion following kidney biopsy in a patient treated with sirolimus.

Case Report: A 32-year-old woman with a history of end-stage renal disease of unknown etiology had undergone right renal transplantation from an unrelated living donor, eight years previously. She was referred to our hospital with dyspnea, localized abdominal pain, and swelling of the transplanted kidney. The symptoms appeared following a kidney biopsy and the replacement of cyclosporin with sirolimus four months previously. On examination, she had localized swelling of the abdominal wall overlying the transplanted kidney, and a right pleural effusion. Hydronephrosis and nephrotic syndrome were excluded as causes of kidney enlargement. Following the withdrawal of sirolimus therapy her symptoms resolved within three months.

Conclusions: A case is described of lymphedema of the transplanted kidney and abdominal wall with ipsilateral pleural effusion following kidney biopsy attributed to her change in anti-rejection therapy to sirolimus. This case report should raise awareness of this unusual complication of sirolimus anti-rejection therapy and its possible effects on the lymphatic system.

MeSH Keywords: Abdominal Wall • Kidney Transplantation • Lymphedema • Pleural Effusion • Sirolimus • TOR Serine-Threonine Kinases

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Background

Inhibitors of the mammalian target of rapamycin (mTOR) are increasingly used as immunosuppressive agents in organ transplant recipients, especially when a calcineurin–free regimen with less renal toxicity is desired. However, mTOR inhibitors, including sirolimus, are reported to be associated with a variety of adverse effects that include impaired wound healing [1], interstitial pneumonitis [2], anemia, hyperlipidemia [3], vascular thrombosis [4], ascites, lymphocele, peripheral edema, and pleural effusion [5].

This report describes a case of sirolimus-induced pleural effusion and enlargement of a transplanted kidney presenting with abdominal pain and swelling following routine renal needle biopsy and following the replacement of cyclosporin with sirolimus anti-rejection therapy. Hydronephrosis and nephrotic syndrome were excluded as causes of kidney enlargement. The patient's symptoms improved following discontinuation of sirolimus and completely resolved within the following three months. To our knowledge, this is the first case of sirolimus-induced lymphedema of the transplanted kidney and abdominal wall with ipsilateral pleural effusion following kidney biopsy.

Case Report

A 32-year-old woman with a history of end-stage renal disease of unknown etiology had undergone renal transplantation from an unrelated living donor, eight years previously. She was referred to our hospital with dyspnea, localized abdominal pain, and swelling of the transplanted kidney. The symptoms appeared several days following a kidney biopsy and the replacement of cyclosporin with sirolimus.

Four months before admission to our hospital, a kidney biopsy had been performed for asymptomatic proteinuria and mild allograft dysfunction. The blood creatinine level at the time of performing the needle biopsy was 1.4 mg/dL. The histopathology findings from the renal biopsy included proliferative glomerulonephritis and suspected cyclosporin toxicity. Following the renal biopsy results, cyclosporin treatment was switched to sirolimus, 1 mg twice a day. Her other maintenance immunosuppressive therapy included prednisone and mycophenolate. Several days after the kidney biopsy procedure and change to sirolimus therapy, swelling and pain appeared at the site of the kidney biopsy in the right lower abdominal quadrant and progressed over the following four weeks. She developed symptoms of dyspnea two weeks before admission to our hospital.

On hospital admission, physical examination showed a normal blood pressure, reduced breath sounds over the lower and central the right lung, localized non-pitting swelling, and tenderness of the right lower abdomen associated with an enlarged right-sided transplanted kidney. Fever, peripheral edema, ascites, lymphadenopathy, or organomegaly were not detected. Chest X-ray confirmed a right-sided pleural effusion. During her hospital admission, the pleural effusion required frequent drainage, due to fluid re-accumulation and associated dyspnea.

The results of laboratory investigations showed mild anemia, proteinuria, and a transudate pleural effusion (Table 1). Serum and pleural fluid creatinine levels were 1.2 mg/dL and 1.0 mg/dL, respectively. The serum sirolimus base level was 15.6 ng/mL. The creatinine level remained at a constant level during the patient's hospital admission. While the length of the transplanted right kidney, measured by abdominal ultrasonography (US) was 120×62 mm at the time of performing the kidney biopsy four months previously; on the day of hospital admission, the right kidney was 160×83 mm in length. Ultrasound-guided aspiration of a small collection of perinephric fluid was unsuccessful.

Other clinical findings included normal echocardiography, no abnormalities in Doppler ultrasound of the renal vessels, the absence of pulmonary emboli in chest CT angiography, and no urinary leak was detected on diuretic-enhanced 99mTc (DTPA) renal scan. However, the spiral CT scans of the chest, abdomen, and pelvis showed a massive right-sided pleural effusion with adjacent lung atelectasis, normal lung parenchyma, and enlarged right transplanted kidney, localized edema of the abdominal wall, and fluid accumulation suggesting hydronephrosis (Figures 1, 2). The renal DTPA scan and further radiological examination with intravenous contrast did not confirm hydronephrosis (Figure 3). Therefore, both hydronephrosis and nephrotic syndrome were excluded as causes of kidney enlargement.

In the absence of any other causes, sirolimus was believed to be the cause of the complications found in this patient, was replaced with tacrolimus, and the patient was discharged from hospital. The abdominal swelling and pleural effusion reduced, and ultimately resolved, in a period of three months after discharge from hospital. In her last follow-up, two years after discontinuation of sirolimus, we did not detect any kidney enlargement or fluid collection around the transplanted kidney. Renal ultrasound showed that the right kidney was 127 mm in length, and urine protein was <800 mg/24 hours.

Discussion

Treatment of transplant patients with the mammalian target of rapamycin (mTOR) inhibitors, sirolimus or everolimus, have been reported to be associated with increased incidence of

Table 1. Laboratory findings of a 32-year-old woman with pain and swelling of the transplanted kidney, edema of the overlying abdominal wall, and ipsilateral pleural effusion.

Parameters	Value
Blood parameters	
White blood cell (cells/µlit)	8800
Polymorphonuclears (%)	65
Lymphocytes (%)	28
Hgb (g/dl)	11.4
Platelet (×10³ cells/µlit)	312
ESR (mm/h)	25
Fasting blood sugar (mg/dl)	88
Urea (mg/dl)	36
Creatinine (mg/dl)	1.2
Na (mEq/lit)	143
K (mEq/lit)	4.1
AST (IU/lit)	12
ALT (IU/lit)	13
Calcium (mg/dl)	8.2
Phosphorous (mg/dl)	4.4
Total Protein (g/dl)	6.4
Albumin (g/dl)	3.4

Parameters	Value
Urine analysis	
Specific gravity	1.017
PH	5
Protein	+++
White blood cells/HPF*	2–3
Red blood cells/HPF*	1–2
Casts	Negative
Urine protein (mg/24 hours)	2125
Pleural fluid analysis	
Sugar (mg/dl)	114
Cholesterol (mg/dl)	17
Triglyceride (mg/dl)	5
Albumin (g/dl)	0.7
LDH (U/lit)	92
ADA (U/lit)	14
PH	7.49
Red blood cells/HPF*	1000
White blood cells/HPF*	400
Polymorphonuclears (%)	57
Lymphocytes (%)	43

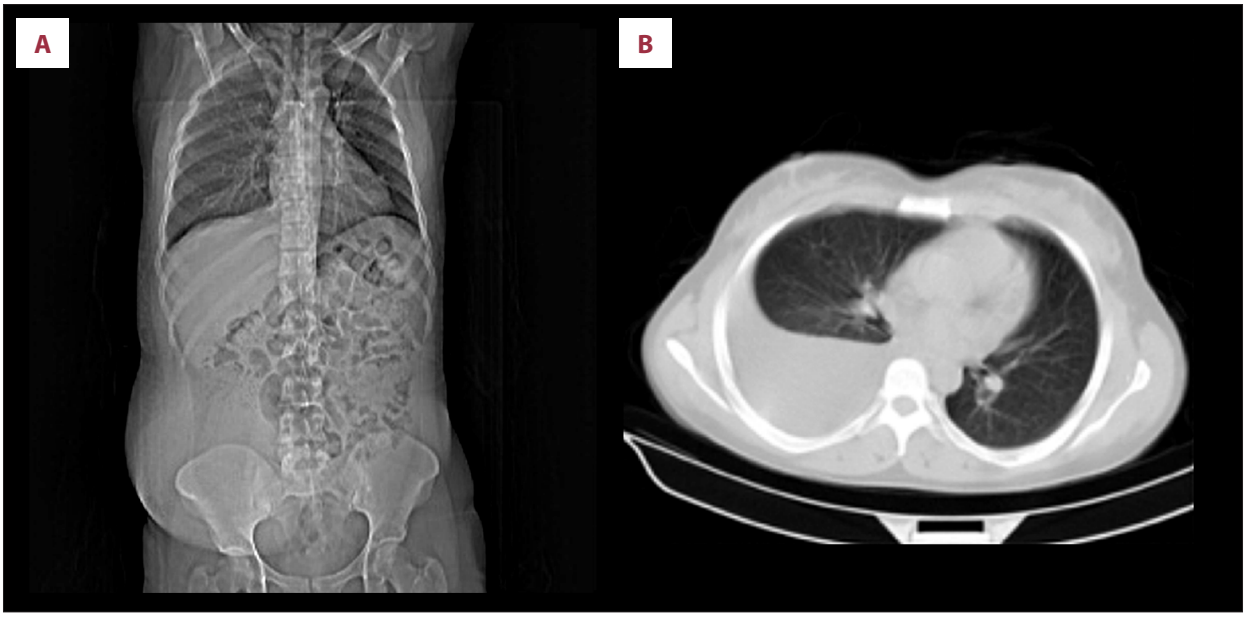

Figure 1. (**A, B**) Right sided pleural effusion and abdominal wall swelling in CT-Scan of a 32-year woman with sirolimus-induced lymphedema, suffering from dyspnea as well as pain and swelling over the transplanted kidney developing after undergoing a kidney biopsy.

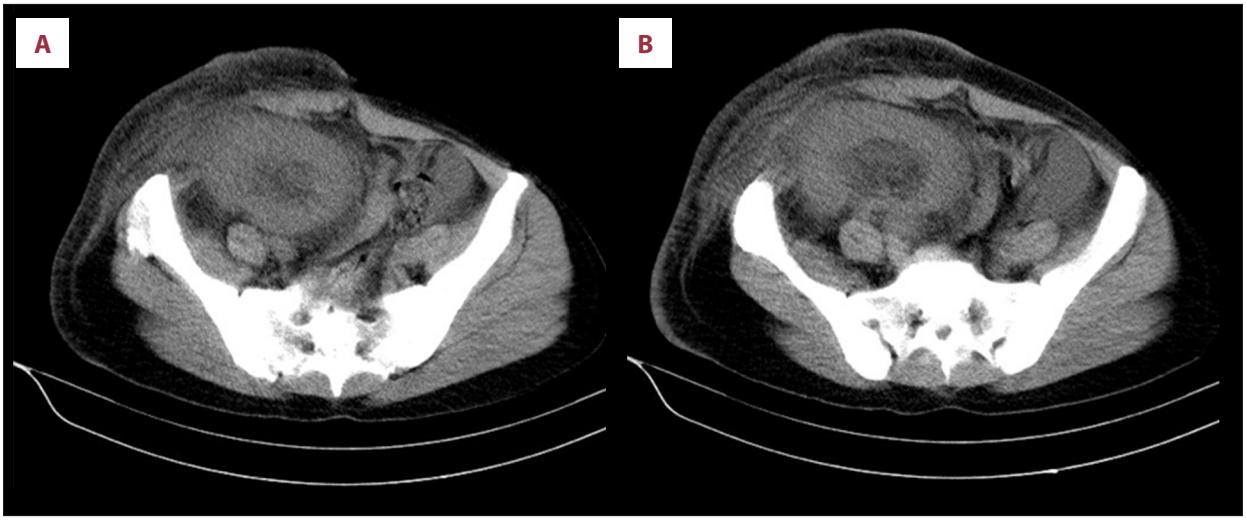

Figure 2. (**A, B**) Abdominal and pelvic CT-Scan of a 32-year -woman showing severe enlargement of transplanted kidney and edematous abdominal wall. This CT scan demonstrates intra-pelvis fluid accumulation that firstly suspected to be hydronephrosis.

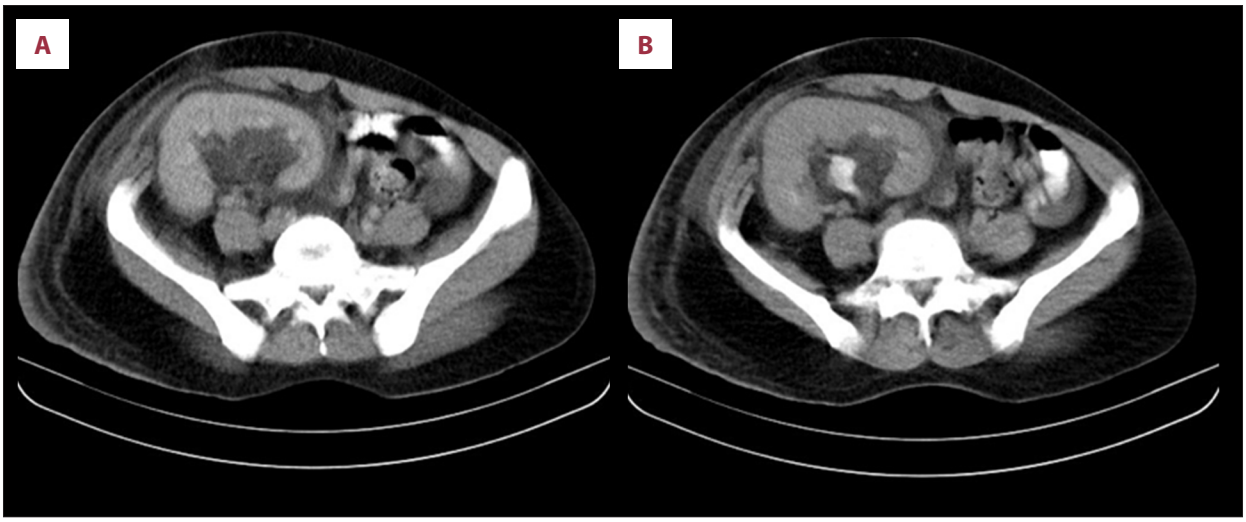

Figure 3. (**A, B**) Contrast-enhanced abdominal and pelvic computed tomography (CT) scan of a 32-year-old woman showing enlargement of the transplanted kidney and no hydronephrosis.

lymphocele following kidney transplantation surgery [5]. This finding is suggestive of the potential of mTOR inhibitors to prevent the healing of lymphatic channels damaged during surgery. Furthermore, mTOR inhibitors can create localized or generalized lymphedema in different parts of the body at any time after transplantation [5–20]. The exact pathophysiology of lymphedema attributed to mTOR inhibitors is not understood, but mTOR inhibition has been shown to blocks cytokine-mediated T-cell proliferation, and this is the basis for their clinical use in preventing organ transplant rejection.

However, the activity of sirolimus is not limited to the immune system. Studies on lymphangiogenesis have shown that delayed surgical wound repair and closure of disrupted lymphatic vessels are unwanted consequences of mTOR inhibition [21]. Damage to the lymphatic drainage by trauma, surgery, infection, chronic inflammation, or cancer is followed by the proliferation and migration of damaged lymphatic endothelial cells through the stimulation of endothelial cell growth factors, including VEGF-A and VEGF-C, and inhibitors of mTOR may prevent this process and lead to impaired reconstruction of lymphatic channels [21]. Also, recent studies have shown that sirolimus may increase capillary permeability, and the resultant overproduction of lymphatic fluid enhances interstitial pressure leading to compression of lymphatic vessels [6]. Localized lymphedema, secondary to sirolimus or everolimus treatment, has been reported to involve the extremities, but other locations such as eyelid, face, breast, and flanks can be

affected [5–20]. Swelling of tissues associated with sirolimus treatment has been reported either as an isolated, localized lymphedema, or with edema of the extremities.

A review of the literature has shown that only 28 case reports of lymphedema of the extremities have been published following the use of mTOR inhibitors (Table 2). In most of these patients, lymphedema was unilateral or asymmetrical, and it was differentiated from other causes of edema based on information provided by lymphoscintigraphy, lymphangiography, or clinical findings. The involvement of the upper extremities was reported in 14 patients, all of whom had unilateral findings; in nine cases, an arteriovenous (AV) fistula was found in the affected limb. The contribution of AV fistula in potentiating the development of lymphedema associated with sirolimus may be related to the surgical damage of the lymphatic system being associated with high venous pressure and the resultant increased lymphatic load.

In this report, we described the case of a young woman with a painful, enlarged transplanted kidney and abdominal wall swelling, whose symptoms commenced following needle biopsy of the kidney and who then developed abdominal wall edema and transudate pleural effusion. The results of renal scintigraphy and the measurement of pleural fluid creatinine did not provide evidence for biopsy-induced urinary tract rupture or urinothorax. Histology of the kidney showed no evidence of an infiltrative process, such as lymphoma. Because the symptoms in this patient commenced after initiating sirolimus treatment and resolved within three months after sirolimus treatment withdrawal, we believe that sirolimus was the cause of the patient's symptoms and that by prevention of repair of lymphatic vessels that may have been damaged during the procedure of kidney biopsy.

Renal biopsy has previously been reported to cause damage to lymphatic structures. Kulkarini et al. reported the development of severe ascites in a patient with a kidney transplant, two weeks after performing a kidney biopsy for a high serum creatinine, and simultaneous replacement of tacrolimus with sirolimus [22]. The patient required twice-weekly therapeutic paracentesis, and lymphangiography and laparoscopy showed a subcapsular lymphocele and lymph leak from the capsular rupture at the site of the kidney biopsy [22]. In another patient with a history of kidney transplantation receiving sirolimus, impaired lymphatic reconstruction was reported after laparoscopic cholecystectomy leading to the development of chylous ascites two months following the procedure; the ascites resolved a month after sirolimus withdrawal [23]. Damasiewicz et al. reported unilateral lymphedema of the upper limb appearing two weeks after an insect bite in a limb with AV fistula in a patient with kidney transplantation receiving sirolimus [14]. We did not confirm lymphatic congestion of the abdominal wall with lymphoscintigraphy in the patient reported in this case, but have not found any other explanation for a non-pitting painful localized abdominal wall swelling in a patient receiving sirolimus, a medication with well-known effects on the lymphatic system.

Pleural effusion has previously been reported as a complication of sirolimus treatment. In this case report, the patient's pleural effusion developed in association with other symptoms and became so severe that it required frequent pleural fluid drainage. Because the pleural effusion and other clinical abnormalities of this patient completely resolved following the withdrawal of sirolimus treatment, we conclude that this complication was attributed to sirolimus. Although pleural effusion, ascites, and lymphocele have previously been reported as complications of the use of mTOR inhibitors [5,25], to the best of our knowledge sirolimus-induced lymphatic congestion of internal organs has never been previously reported. In this case presentation, severe enlargement of the transplanted kidney could have been due to lymphatic congestion of the transplanted kidney. A normal kidney has two connected lymphatic systems; the first drains lymph from the cortex to the subcapsular networks and perinephric lymphatics; the second is the hilar system that collects lymph from the renal cortex and medulla to the hilar lymphatic ducts, and so ligation of hilar lymphatic ducts during surgery leads to drainage of lymph through subcapsular lymphatics [24]. After surgery, lymphangiogenesis can connect perinephric lymphatics to the lymphatics of the abdominal wall, and this may be an explanation for simultaneous congestion and swelling of the kidney and overlying abdominal wall, as well as the development of ipsilateral pleural effusion in our patient.

A review of the literature has shown that there have been few case reports of lymphatic disorders of native kidneys, or renal lymphangiectasia, characterized by insufficient lymphatic drainage of the kidney due to the failure of communication between the lymphatics of the kidney and with larger retroperitoneal lymphatic ducts [26,27]. The resulting ectasia of lymphatic spaces may lead to enlargement of the kidney, as well as cyst formation or lymph accumulation in renal sinuses and perinephric spaces, but the pathophysiology of this disorder is still unknown and relies on information from case reports. Inflammation, infection, trauma, or malignancy have been suggested as the etiologies of the acquired forms of this disorder [26,27]. However, sirolimus and kidney biopsy has not been previously reported as the cause of lymphangiectasia of the native kidney.

There were some similarities in the clinical presentation, including the association with pleural effusion, and the radiologic findings of our patient, with those seen in lymphangiectasia of native kidneys, and it is possible that our patient may

Table 2. Literature review of previously reported cases of mammalian target of rapamycin (mTOR) inhibitor-induced lymphedema of the extremities.

Ref	age/sex	TO	Sirolimus level (ng/ml)	Duration of receiving mTOR inhibitors before development of edema (months)	Location of lymphedema	Probable predisposing factor	Action taken regarding mTOR administration after development of edema	Outcome/after DC or DR of sirolimus
[6]	37/F	K	5–15	3	BLE, LUE, LB	LUE AV-fistula	DC	R/a few months
	58/F	K	5–15	6	BLE, RUE, RB	RUE AV-fistula	DC	PI/a few months
	63/F	K	5–15	3	BLE (left >right)		DC	PI/a few months
[7]	23/F	K	26.3	24	LUE, LB	LUE AV-fistula	DR	SI
	53/M	K	8.8	6	RUE, RB, RLE	RUE AV-fistula	DC	SI
[8]	71/M	H	<2.5	48	Face, RUE	Eyelid excision due to carcinoma	DC	R/6 weeks
[9]	26/M	K	10–18	30	LUE		DC	SI
	26/F	K	10–15	30	LLE		DC	SI/a few months
	30/M	K	10–18	24	LUE		DC	SI/a few months
	49/M	K	10–16	7	RUE		DC	SI/a few months
[10]	59/M	L		7	RLE		DC	R within 3 months
[11]	56/F	K	11.1	3	BLE (right>left), Ascites, Pleural and pericardial effusion, Lymphocele		DR, D, then DC	R/3 months
[12]	68/M	H	8	1*	RUE		DC*	R/2 months
[13]	57/M	K	NA	9	RLE, Right flank	LUE AV-fistula	DC after 12 months	NI/4 years
	23/F	K	NA	6	BLE, LB	RUE AV-fistulaO	DC after 9 months	NI/2 years
	44/M	K	NA	3	BLE, Genitalia	and cellulitis	DC after 11 months	SI
	49/F	K	NA	10	LLE		DC after 12 months	NI/6 years
	62/M	L	NA	3	RLE		DC at month 3	NI
	43/M	K	NA	3	LLE		DC at month 6	NI
	44/F	K	NA	7	LUE, Left flank, LB		DC after 52 months	NI
	53/F	K	NA	5	RUE, Right flank, RB		DC after 16 months	NI
[14]	59/F	K	6–10	30	LUE	LUE AV-fistula, insect bite of LUE	DC after 5 months, ligation of fistula	SI/4 weeks
[15]	52/F	K	6.3–10.5	NA	LLE		DC after several months	SI/2 weeks
[16]	60/F	K	**	6	LUE, LLE, left breast		DC after 3 months	R/after 3 months
[17]	40S/M	K		A few months	LUE	LUE AV-fistula	DC	PI
	40S/F	K		12 months	RUE, RB	RUE AV-fistula	NA	NI/5years
[18]	14/F	I	NA	8	BLE, LUE		DC, compression therapy	PI/6 months
[19]	42/M	K	3.8–11.3	13	BLE (left >right)	Bilateral central femoral catheterization	DC after 4.5 years	MI

R – references; TO – transplanted organ; K – kidney; H – heart; L – liver; I – intestine; BLE, RLE and LLE – bilateral, right and left lower extremities, respectively; LUE, RUE – left and right upper extremity, respectively; RB – right breast; LB – left breast; DC – discontinuation; DR – dose reduction; D – diuretics; R – Resolving edema; NI, MI, PI and SI – no, mild, partial and significant improvement, respectively; NA – not available. * The edema developed after everolimus consumption, worsened with switching to sirolimus and improved with discontinuation of mTORs. ** The patient was on everolimus.

be the first case of renal lymphangiectasia in a transplanted kidney. In this report, the patient presented with pleural effusion on the same side as the enlarged transplanted kidney, the pleural fluid was clear, a transudate, as in previously reported rare case reports of renal lymphangiectasia. These findings may indicate a renal origin for the pleural fluid with a low lipid and protein concentration [26,27]. In some case reports, renal lymphangiectasia has led to proteinuria or deterioration of renal function [26]. In our patient, proteinuria worsened after the appearance of symptoms and reduced following sirolimus withdrawal.

In previously reported cases of mTOR inhibitor-induced lymphedema, early withdrawal of the medication led to partial or complete resolution of edema after several months. Our patient's symptoms resolved within three months after discontinuation of sirolimus. However, in some patients, especially when mTOR inhibitor consumption continued for a longer period after the appearance of symptoms, cessation of the treatment had no significant effect on improvement of edema (Table 2). Hence early cessation of therapy may prevent irreversible damage to lymphatic tissues.

Conclusions

Lymphedema in the skin of the extremities, abdominal wall, face, and breast, have previously been reported as a relatively rare complication of mTOR inhibitor use but may involve internal organs such as the kidney. In patients treated with sirolimus, lymphatic damage caused by kidney needle biopsy may be a predisposing factor for this complication. This case report has shown that lymphedema of the transplanted kidney can involve the adjacent abdominal wall and become associated with an ipsilateral pleural effusion. Therefore, transplant clinicians should be made aware of this unusual complication of mTOR inhibitor therapy to prevent unnecessary and expensive investigations and to allow for a decision to be taken regarding discontinuing sirolimus anti-rejection therapy.

Conflict of interest

None.

References:

1. Troppmann C, Pierce JL, Gandhi MM et al: Higher surgical wound complication rates with sirolimus immunosuppression after kidney transplantation: A matched-pair pilot study. Transplantation, 2003; 76(2): 426–29
2. Morelon E, Stern M, Kreis H: Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. N Engl J Med, 2000; 343(3): 225–26
3. Merkel S, Mogilevskaja N, Mengel M et al: Side effects of sirolimus. Transplant Proc, 2006; 38(3): 714–15
4. Barone GW, Gurley BJ, Abul-Ezz SR et al: Sirolimus induced thrombotic microangiopathy in a renal transplant recipient. Am J Kidney Dis, 2003; 2: 202–6
5. Gharbi C, Gueutin V, Izzedine H: Oedema, solid organ transplantation and mammalian target of rapamycin inhibitor/proliferation signal inhibitors (mTOR-I/PSIs). Clin Kidney J, 2014; 7(2): 115–20
6. Aboujaoude W, Milgrom ML, Govani MV: Lymphedema associated with sirolimus in renal transplant recipients. Transplantation, 2004; 77(7): 1094–96
7. Romagnoli J, Citterio F, Nanni G et al: Severe limb edema in sirolimus-treated patients. Transplant Proc, 2005; 37(2): 834–36
8. Papali A, Giannetti N, Cantarovich M: Unilateral upper extremity edema associated with sirolimus in a heart transplant patient. Transplantation 2007; 83(2): 240
9. Al-Otaibi T, Ahamed N, Nampoory MR et al: Lymphedema: An unusual complication of sirolimus therapy. Transplantation Proc, 2007; 39(4): 1207–10
10. Van Onna M, Geerts A, Van Vlierberghe H et al: One-sided limb lymphedema in a liver transplant recipient receiving sirolimus. Acta Gastroentrol Belg, 2007; 70(4): 357–59
11. De Bartolomeis C, Collini A, Rumberger B et al: Generalized lymphedema in a sirolimus-treated renal transplant patient. Clin Transplant, 2008; 22(2): 254–57
12. Moro JA, Almenar L, Martínez-Dolz L, Salvador A: mTOR inhibitors and unilateral edema. Rev Esp Cardiol, 2008; 61(9): 985–93
13. Desai N, Heenan S, Mortimer PS: Sirolimus-associated lymphoedema: Eight new cases and a proposed mechanism. Br J Dermatol, 2009; 160(6): 1322–26
14. Damasiewicz MJ, Ierino FL: Unilateral upper limb lympatic obstruction and severe lymphoedema in a patient on long-term sirolimus. Nephrology, 2010; 15(8): 779–80
15. Thanaraj V, Woywodt A, Anderton J: A transplant patient with a swollen leg. Clin Kidney J, 2012; 5(5): 467–70
16. Ersoy A, Koca N: Everolimus-induced lymphedema in a renal transplant recipient: A case report. Exp Clin Transplant, 2012; 10(3): 296–98
17. Baliu C, Esforzado N, Campistol JM, Mascaró JM Jr.: Chronic lymphedema in renal transplant recipients under immunosuppression with sirolimus: presentation of 2 cases. JAMA Dermatol, 2014; 150(9): 1023–24
18. Eyigor S, Donmez U, Kilinc S et al: Lymphedema treatment in a patient with a history of intestinal transplantation and mesenchymal stem cell transplantation. Turk J Phys Med Rehab, 2015; 61: 84–88
19. Motse KG, Mashabane MJ: Sirolimus-induced lymphoedema. S Afr Med J, 2016; 106(9): 886–87
20. Hille U, Soergel P, Makowski L et al: Lymphedema of the breast as a symptom of internal diseases or side effect of mTor inhibitors. Lymphat Res Biol, 2012; 10(2): 63–73
21. Huber S, Bruns CJ, Schmid G et al: Inhibition of the mammalian target of rapamycin impedes lymphangiogenesis. Kidney Int, 2007; 71: 771–77
22. Kulkarni S, Burns A, Al-Akraa M: Severe ascites following renal transplant biopsy caused by a rupture of a subcapsular lymphocele: Treated successfully by retroperitonealization. Nephrol Dial Transplant, 2004; 19(4): 1022–23
23. Castro G, Freitas C, Beirão I et al: Chylous ascites in a renal transplant recipient under sirolimus (rapamycin) treatment. Transplant Proc, 2008; 40(5): 1756–58
24. Ranghino A, Segoloni GP, Lasaponara F, Biancone L: Lymphatic disorders after renal transplantation: New insights for an old complication. Clin Kidney J, 2015; 8(5): 615–22
25. Kan HJ, Heuvers ME, Grijm K, van Hal PT: Sirolimus-related dyspnoea, airway obstruction and pleural effusion after lung transplantation.Transpl Int, 2009; 22(9): 940–42
26. Bazari H, Attar EC, Dahl DM et al: Case records of the Massachusetts General Hospital. Case 23-2010. A 49-year-old man with erythrocytosis, perinephric fluid collections, and renal failure. N Engl J Med, 2010; 363(5): 463–75
27. Viglietti D, Sverzut JM, Peraldi MN: Perirenal fluid collections and monoclonal gammopathy. Nephrol Dial Transplant, 2012; 27(1): 448–49