

Lymphedema secondary to idiopathic occlusion of the subclavian and innominate veins after renal transplantation

A case report

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Abstract

Rationale: Among the causes of swelling in the extremities of renal transplantation patients, secondary lymphedema caused by complete idiopathic obstruction of large veins is rare and may be difficult to diagnose and treat.

Patient concerns: A 64-year-old man presented with severe edema and pain that occurred suddenly in the right arm.

Diagnoses: The patient was diagnosed as stage-2 secondary lymphedema caused by idiopathic occlusion of the subclavian and innominate veins.

Interventions: Lymphoscintigraphy and ascending venography of the right arm confirmed the diagnosis. Intensive complete decongestive therapy for lymphedema was performed.

Outcomes: Following 2 weeks of active rehabilitation, the pain level and edema status were significantly improved.

Lessons: When idiopathic swelling of the extremities occurs in renal transplant patients, secondary lymphedema caused by venous occlusion may be the cause. When direct intervention for the venous occlusion proves to be difficult, a conservative approach may be helpful.

Abbreviations: AVF = arteriovenous fistula, BUN = blood urea nitrogen, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, ESR = erythrocyte sedimentation rate, mTOR = mammalian target of rapamycin, VAS = visual analog scale, WBC = white blood cells.

Keywords: complete decongestive therapy, lymphedema, renal transplantation, venous occlusive disorder

1. Introduction

Renal transplant patients may often encounter various circumstances that may compromise the lymphatic system. Among the various lymphatic complications that may occur, lymphedema is not easily diagnosed as it must be differentiated from edema due to other conditions that may occur after renal transplantation.

Editor: N/A.

Funding: This research was supported by the Soonchunhyang University Research Fund.

Patient consent: Written consent was obtained from the patient.

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:48(e8942)

Received: 25 September 2017 / Received in final form: 1 November 2017 /

Accepted: 8 November 2017

<http://dx.doi.org/10.1097/MD.0000000000008942>

Lymphedema causes a change in appearance due to localized fluid retention in the skin tissue, and it may also cause serious psychological problems such as depression, anxiety, and adjustment disorders.^[1,2] The major known causes of typical lymphedema include lymph node dissection, surgery, radiation, trauma, and lymphatic filariasis.^[3–7] However, the causes of lymphatic complications that occur after renal transplantation include the following: first, surgical damage to lymphatics directly related to the transplantation;^[8] second, medical causes such as use of immunosuppressive drugs and rejection episodes;^[8,9] and third, deep vein thrombosis or venous stenosis/occlusion caused by various venous procedures performed for dialysis access before renal transplantation.^[10] This report involves a rare case of a secondary lymphedema caused by complete idiopathic obstruction of large veins in the arm of a renal transplant patient that had been healthy for several years following arteriovenous fistula (AVF) removal. To the best of our knowledge, there are no articles that have reported such a case. Accordingly, we are reporting our approach to systematically diagnosing this case and treating it with nonsurgical methods, along with a literature review.

2. Case presentation

A 64-year old male patient visited our hospital with severe edema that had occurred suddenly in his right arm. The patient had been on hemodialysis since being diagnosed with end-stage renal

Table 1
Difference in circumferences of both upper extremities after 2 weeks of rehabilitation.

Measurement sites	Difference in circumference, cm	
	Pretreatment	Posttreatment
Above elbow*	4.6	1.1
Elbow†	5.7	3.2
Below elbow‡	5.6	4.1
Wrist§	4.5	3.3
MCP joint	4.8	3.5

* 15 cm proximal to the lateral epicondyle of the humerus.

† The elbow, the mid-point between the medial and lateral epicondyle.

‡ 10 cm distal to the lateral epicondyle.

§ The wrist, the mid-point of the wrist crease.

MCP = metacarpophalangeal.

disease 19 years earlier. In the initial stage, an AVF of the right upper arm was used, but after 1 year, an AVF of the left upper arm was used instead. Upon receiving a renal transplant 6 years ago, hemodialysis was discontinued and the AVF in the right arm was removed. Until recently, there was no cause for the edema in the right arm, such as local infection, injury, or vascular procedures. The clinical examination performed upon admission showed severe edema from the right axilla to the finger tips. Moreover, there was a positive stemmer sign in the right hand, progression of fibrotic changes in the right forearm, and numerous collateral vessels in the neck and anterior chest wall. The patient complained of ambiguous pain across the right upper arm and the entire hand, corresponding to a score of 6 on the visual analog scale (VAS). In addition, the circumferences of 5 measurement sites showed differences of ≥ 4.5 cm between the right and left arms (Table 1).^[11,12] To find the cause of upper extremity edema, a blood test was performed to check kidney function and possible thrombus or infections while radiological imaging was used to check for fractures, hemorrhage, and vascular and lymphatic anomalies. Among these, ascending venography showed complete occlusion of the right subclavian and innominate veins as well as collateral circulation in the surrounding deep vessels (Fig. 1). Lymphoscintigraphy showed mild dermal backflow at the right forearm and decreased uptake of the right axillary lymph nodes, based on which, lymphedema caused by lymphatic obstruction was diagnosed (Fig. 2). Other

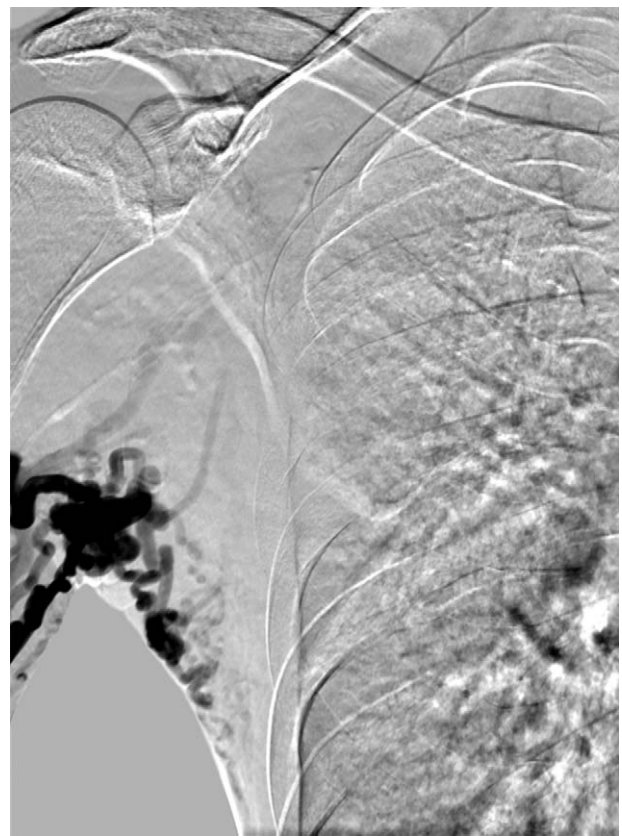


Figure 1. Ascending venography of the right arm showing complete occlusion of the right subclavian and innominate veins. The blood flows into the deep veins through the collateral circulation.

blood test results are shown in Table 2 and there were no abnormal findings suggestive of ipsilateral edema of the upper extremities. In conclusion, the final diagnosis made was stage-2 secondary lymphedema caused by complete occlusion of the innominate and the right subclavian veins.^[13] A nonsurgical approach was chosen as the treatment strategy after multidisciplinary discussion. The treatment included aggressive manual lymphatic drainage and compression therapy including stocking

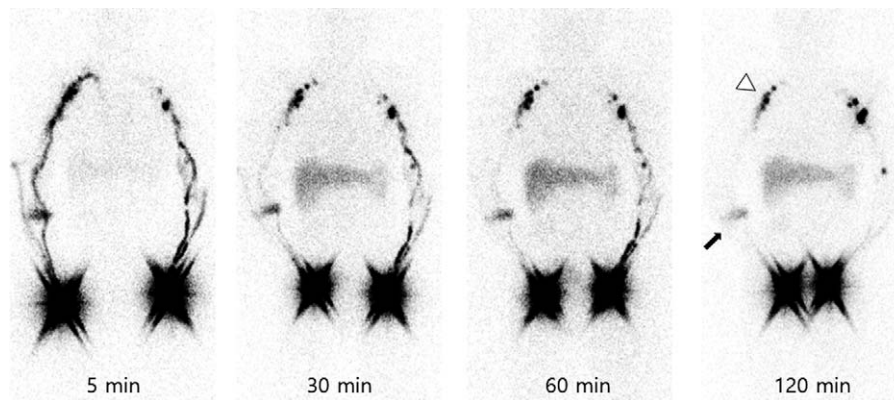


Figure 2. Lymphoscintigraphy of the both upper extremities was obtained at 5, 30, 60, and 120 minutes after intradermal injection of 148 MBq/0.4 mL ^{99m}Tc-phytate into the second and third interdigital space of both hands. The delayed phase (120 minutes) image showing small localized dermal backflow (arrow) at the right forearm level and decreased uptake of the right axillary lymph nodes (arrowhead), suggesting the presence of lymphedema of the right upper extremity.

Table 2**Laboratory findings.**

Values	Results	Normal range
Creatinine, mg/dL	1.60	(0.5–1.2)
eGFR, mL/min	44.86	(>90)
BUN, mg/dL	13.7	(6–20)
Platelet count, 10 ³ /μL	199	(130–450)
WBC count, 10 ³ /μL	7.5	(4.0–10.0)
ESR, mm/hr	20	(0–20)
CRP, mg/dL	0.10	(0.0–0.5)

BUN= blood urea nitrogen, CRP=C-reactive protein, eGFR=estimated glomerular filtration rate, ESR=erythrocyte sedimentation rate, WBC=white blood cells.

and bandage methods, based on the principle of complete decongestive therapy. Accordingly, the patient and his guardian were briefed on the treatment. Following 2 weeks of active rehabilitation, the pain level subsided to VAS 2, and the edema also improved as shown in Table 1. The patient signed informed consents. In our case, the patient accepted regular examinations and proved therapy, so the ethical approval was not necessary.

3. Discussion

This case report involved the sudden onset of edema in the previously healthy arm of a renal transplant patient, which was systematically diagnosed as being a rare case of secondary lymphedema due to complete obstruction of large veins. The patient was successfully treated using noninvasive complete decongestive therapy and patient education. Edemas caused by venous insufficiency must be differentiated from lymphedema, but untreated venous insufficiency may eventually develop into a combined venous/lymphatic disorder, which may also lead to secondary lymphedema. To successfully differentiate between these conditions, it is important to verify any lymphatic flow dysfunction by radiological examinations such as lymphoscintigraphy. Causes of venous insufficiency in the upper extremities may include intravenous inflammation, injury, stenosis, and thrombosis. Among patients with advanced chronic venous disease, 20% to 30% suffer from lymphatic dysfunction associated with recurrent cellulitis.^[14–16] In addition, iatrogenic venous disruption is considered to be a key predisposing factor for lymphedema associated with surgery for breast cancer patients.^[17] Intravenous insertion of wires or devices is known to be a key factor in causing deep vein thrombosis of the upper extremity, and 50% of cases involve central venous line insertion within the prior month.^[18] In addition, venous thrombosis (17%–25%) and stenosis (14%–42%) have been reported as common venous complications of AVF surgery.^[10] However, the AVF in the right arm of the patient in our case had been removed several years ago, there was no history of recent intravenous insertion of central venous lines or devices, and the patient had no complications associated with venous insufficiency. Consequently, venous occlusion was not suspected to be the cause of the edema before conducting the ascending venography. It is extremely rare to find complete idiopathic venous obstruction of large veins occurring in an arm that had been healthy for several years after removal of an AVF that had only been placed for a short period of time ultimately leading to severe stage-2 lymphedema. In order to identify the specific causes of large vein obstruction and to identify morphological anomalies in distal regions, it is necessary to perform additional radiological

Table 3**Reported cases of lymphedema associated with the use of immunosuppressive agents after renal transplantation.**

Authors (year)	Sex	Age, years	Lesion	Drug
De Bartolomeis et al. ^[24]	Female	56	Right leg	Sirolimus
Thanaraj V et al. ^[23]	Female	52	Left leg	Sirolimus
Ersoy et al. ^[25]	Female	60	General	Everolimus
Baliu et al. ^[26]	Male	40	Left arm	Sirolimus

examinations, such as computed tomography angiography. However, no further examination was conducted as it was determined that the venous occlusion was too severe to perform percutaneous transluminal angioplasty and use of a contrast medium may cause damage to the transplanted kidney. The causes of lymphatic complications, including lymphedema, in renal transplant patients are numerous, but they can be largely divided into surgical and medical factors. Surgical factors refer to lymphatic complications caused by damage to the lymphatics near the graft or the iliac vessels during the renal transplantation surgery.^[8] Medical factors are known to include diabetes, rejection episodes, and immunosuppressive drugs.^[8,9] Microangiopathy caused by diabetes may interfere with wound healing after renal transplantation causing lymphatic complications.^[9] Moreover, previous studies have reported that rejection episodes and lymphatic complications are highly correlated.^[20] However, we were unable to present sufficient evidence of pathogenic mechanisms that can explain high incidence of lymphatic complications during rejection.^[20] Several adverse effects of mammalian target of rapamycin (mTOR) inhibitors have been reported including lymphocele, delayed wound healing, and microangiopathy.^[9,21,22] Cases of lymphedema of the extremities due to the use of immunosuppressants after a renal transplantation are rare. Such previously reported cases are summarized in Table 3.^[23–26] The mechanism by which sirolimus interferes with lymphatic drainage is still unclear. However, one hypothesis is that it inhibits lymphangiogenesis by interfering with the activation of intracellular pathways in lymphatic endothelial cells that act as a major initiator of lymphangiogenesis during the postsurgical regeneration period.^[8,27] It is suspected that the antilymphangiogenic effect of the 2 mTOR inhibitors, rapamycin (sirolimus) and RAD-001 (everolimus), may ultimately damage the lymphatic integrity of the entire body.^[8,27] In the present case, however, no lymphatic complications occurred while using tacrolimus and mycophenolic acid after renal transplantation and several years had passed since discontinuing the drug.

Therefore, we believe that there is no association between the drug and the current lymphedema. However, when a patient uses an mTOR inhibitor at an early stage, close attention must be paid to detect any lymphatic complications. If lymphedema does occur, dose reduction or discontinuation of the treatment should be considered to prevent lymphedema from developing to an irreversible condition.^[8]

4. Conclusion

Edema in the extremities of renal transplant patients may be caused due to a wide range of factors, and therefore, a systematic diagnostic approach must be taken. When the underlying cause is secondary lymphedema caused by idiopathic venous occlusion, intensive rehabilitation may be an option for successful treatment.

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