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One-sided limb lymphedema in a liver transplant recipient receiving Sirolimus

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Abstract

Sirolimus (SRL) is associated with many side effects including hypercholesterolemia, anaemia, impaired wound healing and abnormal liver function tests. Limb lymphedema has only been reported several times in renal transplant recipients. We present a case of lower limb lymphedema that occurred in a 59-year-old liver transplant recipient after being on a SRL regimen for seven months. Extensive diagnostic investigations could not reveal signs of infection, venous obstruction or malignancy. After discontinuation of SRL, the lymphedema gradually resolved during the next three months. The pathologic mechanism behind this phenomenon is unknown, but antiangiogenetic and antiproliferative properties of SRL have been hold responsible. Further studies are necessary to explain this rare side effect. (Acta gastroenterol. belg., **2007**, 70, **357-359**).

Key words : peripheral edema, rapamycin, side effects, transplantation, liver.

Introduction

Sirolimus (SRL) is a relatively new immunosuppressive drug that improves the renal function because of less nephrotoxicity compared to the calcineurin inhibitors. Side effects associated with SRL are hypercholesterolemia, decreased blood platelets, anaemia, impaired wound healing, abnormal liver function tests, hypertension, diarrhea and electrolyte disturbances (1,2). Peripheral lymphedema is a rare complication which has been described in kidney transplant recipients (3,4). We describe a liver transplant recipient who developed severe lymphedema of his right lower extremity after being on a SRL regimen for seven months.

Case report

A 59-year-old white male patient received a cadaver donor liver transplant in March 2003 for end-stage alcoholic liver cirrhosis. The patient had ceased drinking two-and-a-half years earlier. The immunosupression regimen after the transplantation consisted of cyclosporin, mycophenolate mofetil and corticosteroids. In September 2003, the patient had an episode of acute graft rejection, which was successfully treated with high doses of corticosteroids and the cyclosporin was changed for tacrolimus. In August 2005, we switched from tacrolimus to SRL because of rising creatinine levels (1.8 mg/dL). Seven months later (March 2006), the patient developed mild swelling of the right lower extremity, for which he was initially treated with furosemide. The edema gradually worsened and became nonpitting during the next months (Fig. 1). The family history for peripheral edema was negative. The right leg measured 41 cm in diameter at the widest point ; the left leg measured 35.5 cm. Lymph drainage therapy relieved symptoms only for a short period of time. Laboratory investigations revealed no hypoalbuminemia or proteinuria. There was no evidence of infection with cytomegalovirus, Epstein-Barr virus or Borrelia burgdorferi. SRL levels stayed within limits during the whole treatment period, with mean levels of 11 ng/ml. Venous duplex ultrasound of the right leg showed extensive subcutaneous edema but was negative for venous obstruction. CT and MRI of the pelvis detected no malignancy or other abnormalities which could cause this lymphedema. Subsequently, SRL was replaced for tacrolimus in July 2006. After three months both legs had the same diameter again (Fig. 2).

Discussion

The prevalence of limb lymphedema in liver transplant recipients related to SRL is unknown. Recently, two case reports described this complication in five renal transplant recipients (3,4). Two patients had swelling and lymphedema of breast and the upper extremity formerly used for hemodialysis access, together with lymphedema of the lower extremities. One patient presented with swelling of the left upper extremity (same side as hemodialysis access). Lymphedema of both upper and lower extremities and only the lower extremities was also reported (3,4). Except for limb lymphedema, eyelid edema that dissolved after discontinuation of SRL has also been described in one case report (5).

The underlying pathologic mechanism that can explain the edema is unknown. It often occurs on the same arm used for hemodialysis access. It has been hypothesized that increased lymph flow together with a disrupted lymphatic system might cause edema (3,4,6). Since renal transplant patients often underwent several

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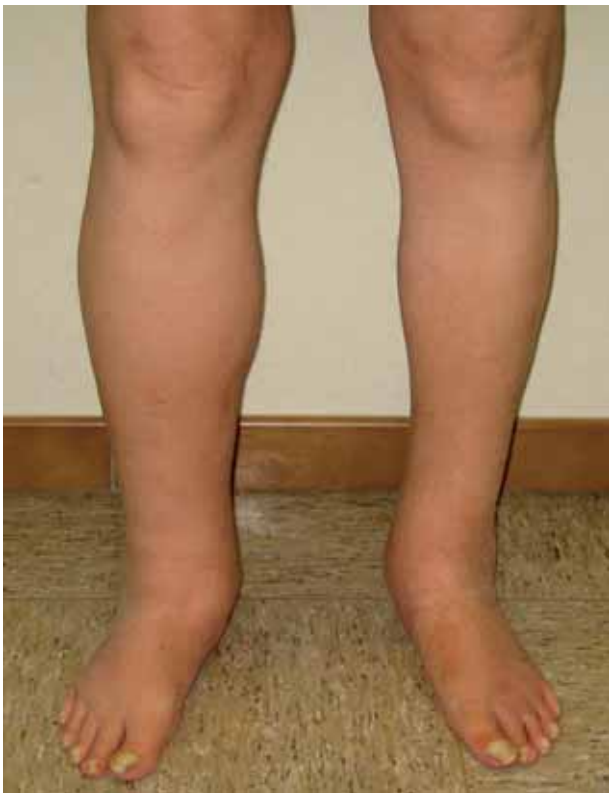

Fig. 1. — Picture of both legs during Sirolimus treatment.
Right-sided limb lymph edema. Diameter of the right leg was 41 cm ; the left leg measured 35.5 cm.

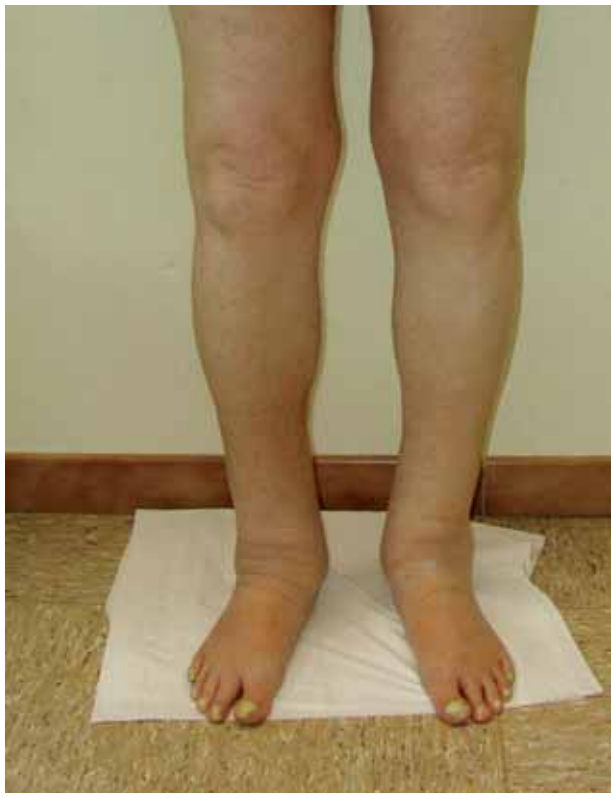

Fig. 2. — Picture of both legs 3 months after discontinuation of Sirolimus.
Resolvement of the lymphedema after 3 months ; the diameter of both legs was 35.5 cm.

procedures to create a sufficient arteriovenous shunt, this mechanism might play a role (3). This hypothesis is consistent with the finding of an increased incidence of lymphocele in patients that used SRL after a kidney transplantation (6,7). A lymphocele is a collection of retroperitoneal lymph around the kidney that originates from dissected iliac or renal lymphatic vessels. The reason why SRL can induce lymphocele formation is not entirely clear, but SRL is known to delay wound repair due to a decrease in production of vascular endothelial growth factor (VEGF) (7,8). VEGF has shown to be a key mediator in tumour lymphangiogenesis, especially VEGF-C (9). Inhibition of VEGF by SRL might be responsible for less blood and lymph vessels, which eventually causes lymphedema. The increased lymph flow might be explained by certain observations seen in rabbit endothelial cells : SRL caused significant release of prostaglandins in these cells (10). Alterations in the production of prostaglandin substances might eventually result in an increased vascular permeability and a secondary increase in lymphatic fluid (3,10).

Except for the fact that our patient is not a renal but a liver transplant recipient, he shared many characteristics with the patients described in the previously mentioned case reports : no signs of malignancy, a negative family history for peripheral edema and a significant delay between intake of SRL and start of symptoms (11 weeks to 3 years) (3,4). Lymphedema in only one extremity (apart from the arm used for hemodialysis access), as in our patient, was not reported. One patient however, developed swelling of both lower extremities and this swelling was significantly worse on the left side (4). We hypothesize that our patient has a congenital or acquired malformation of the lymphatic system of the right lower leg. This would, together with the antiangiogenetic and anti-lymphangiogenetic properties of SRL, made him more susceptible to developing limb lymphedema.

In conclusion, SRL is associated with limb lymphedema that gradually improves after discontinuation. The pathologic mechanism is unknown, but the antiangiogenetic and anti-lymphangiogenetic properties of SRL by inhibition of VEGF may be responsible. Since the safety of SRL in liver transplant recipients has not yet been established, it is recommended that one should closely monitor patients when prescribing this medicine. In this way, peripheral edema but also more life threatening complications can be recognised in an early stage.

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