



# Lymphedema Treatment in a Patient with a History of Intestinal Transplantation and Mesenchymal Stem Cell Transplantation

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## Abstract

Lymphedema is a rare complication of sirolimus treatment in transplantation patients. We present a case of a 14-year-old female patient who developed lymphedema in three extremities. The patient had undergone ileal and colon resections after sustaining a gunshot to her abdomen. Four months after the injury, she had developed a short bowel syndrome and underwent small intestine transplantation from a cadaver and mesenchymal stem cell transplantation to prevent rejection. Because of kidney failure developed at postoperative month 3, mycophenolate mofetil therapy was discontinued and sirolimus therapy was initiated. The patient was monitored under this therapy until postoperative month 11 when she had swelling in both the legs and left arm. Her condition significantly improved with complex decongestive therapy. This is the first case in the literature involving mesenchymal stem cell transplantation together with ileum transplantation. This case is also noteworthy in terms of lymphedema treatment administered and the involvement of three extremities.

**Keywords:** Lymphedema, sirolimus, transplantation, rehabilitation

## Introduction

Sirolimus is an immunosuppressive agent used for the treatment of hematologic malignancy and hamartoma after organ transplantation (1). Although dyslipidemia, thrombocytopenia, and lymphocele occur relatively often after sirolimus therapy, the development of lymphedema associated with sirolimus is a rare complication (2). We have more knowledge about the etiology and treatment of lymphedema that develops after breast surgery. It is not known to what extent the approaches used in classical lymphedema are effective in sirolimus-related lymphedema cases. Here we present a case of a 14-year-old female patient who developed lymphedema in three extremities after sirolimus therapy.

## Case Report

The patient underwent ileum and colon resection because of injuries to the superior mesenteric artery, ileum, and colon she had developed after a firearm wounding; 4 months after the injury, the patient developed short bowel syndrome and underwent small intestine transplantation from a cadaver and mesenchymal stem cell (MSC) transplantation to prevent rejection. The first step for the procedure was to make space for the graft by removing any failed recipient organs. All adhesions were removed. The graft artery was anastomosed to the infrarenal aorta and the graft vein was drained to the infrarenal vena cava. Jejunojejunostomy was performed for oral-side reconstruction of the gastrointestinal tract. Feeding tube gastrostomy was

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performed for postoperative enteral feeding. For anal-side reconstruction, simple ileostomy was preferred. Anti-thymocyte immunoglobulin 5 mg/kg was the induction immunosuppressive treatment that was initiated prior to transplantation. Steroid bolus 10 mg/kg was administered and tapered gradually. At the time of reperfusion, the first dose of MSCs cultured from the patient's bone marrow was injected into the transplanted intestinal artery at a dose of 1,000,000 cells/kg. As for maintenance immunosuppressive therapy, prednisolone, mycophenolate mofetil, and tacrolimus were administered. During follow-up, medical treatment was administered to the wound site infection, catheter infection, or lung infection. At postoperative day 15, a second dose MSCs was administered at the same dose through the peripheral venous route. Because kidney failure developed in the patient at postoperative month 3, tacrolimus therapy was discontinued and sirolimus therapy was initiated (2-3 mg/day depending on the blood level). At postoperative month 8, terminal ileostomy was closed and end-to-side ileosigmoidostomy was performed. The patient was monitored under this therapy until postoperative month 11 when she had swelling in both the legs and left arm. The swelling in the right leg regressed spontaneously within a month, but relapsed after 2 months. No anatomical reason was found in the etiological tests that were performed (arterial and venous Doppler ultrasonography of both upper and lower extremities). There was no sign of infection. Lymphedema developed in the patient 11 months after follow-up, but the treatments against catheter, lung, and wound site infections had been provided within the first 2 postoperative months. The patient had no complaints or family history of lymphedema prior to this disease. The lymphedema could not be attributed to any cause other than sirolimus. Considering this could be the reason, sirolimus therapy, which was received by the patient for 34 weeks, was discontinued. The patient presented to our physical therapy and rehabilitation lymphedema diagnosis and therapy center in the 6<sup>th</sup> month of her swelling complaint. The patient was examined by our physical therapy and rehabilitation specialist. Her examination revealed that there was swelling in her legs and the left arm, and the other system examinations were normal (Figure 1). The patient was assessed for lymphedema on the basis of her history, physical examination inspection, palpation, circumference measurements, and volume calculations in line with the International Society of Lymphology guidelines. We used a computer software to convert these values to limb volumes (Limb volumes professional version 5.0) in milliliters. The patient was diagnosed with lymphedema and was suggested to wear a lymphedema compression garment for her left upper extremity. Because the difference of diameter does not require the compression bandage step of the complete decongestive therapy (CDT), its steps outside bandage (skin care, self-massage, compression, exercise, and diet) were administered. CDT treatment (phase 1) was planned for both of her lower extremities. The patient was treated with CDT, which consisted of patient education, manual lymphatic drainage (self-massage, compression therapy with a short stretch bandage for 23 h per day), exercise, and skin care in the intensive phase. In the maintenance phase, compression ban-



Figure 1. Pre-treatment photo of the leg

dages were replaced by low-stretch elastic garments. Compression therapy with a short-stretch bandage was administered to both legs 5 days a week. Treatment continued during weekends without removing the bandage. The patient's treatment in the clinic lasted 45 min to 1 h. During the intensive phase, limb volumes were recorded at 1-week intervals. No drugs or pneumatic compression devices were used for lymphedema. The patient was also advised not to gain weight and to follow an appropriate diet. The patient was given a brochure detailing the treatment program, with suggestions to protect from lymphedema, exercise images, and frequently asked questions. The therapies were administered and measurements were performed by the same physiotherapist, and her response to the treatment was assessed by the same physical therapy specialist. The measurements repeated after 5 months of treatment at our clinic showed that there were decreases in 22.3% and 14.1% of the volumes of the right leg and left leg, respectively (Figure 2). The swelling in the left arm disappeared as a result of the treatment with the lymphedema compression garment. The follow-up examination of the patient revealed the development of a swelling in her genital region. It responded to the external compression with the foam pad and massage therapy. The external pad applied to this region was prepared by the therapist by cutting the foam in a way to exert compression to the genital site and covering



Figure 2. Post-treatment photo of the patient

it with gauze. A corset extending up to the abdominal area and coming down to the thighs was also suggested. The patient and her family were also explained about compression-producing activities such as cycling, sitting on a ball, and lying face down as well as things to be careful about when performing these activities. The patient is still being monitored quarterly under a complex decongestive therapy appropriate for her maintenance period. The patient was informed about the presentation and signed informed consent was obtained.

## Discussion

A child with lymphedema may have either a primary defect of the lymphatics or a secondary (acquired) defect. Lymphedema attributable to an acquired dysfunction of the lymphatic system may be caused by a wide range of conditions such as cancer and its treatment, infection, and autoimmune diseases (3). Considering the patient's personal and family history, she was not suspected of having primary lymphedema. Neither the development of lymphedema nor the clinical monitoring of the patient could be linked to any infection. However, general causes of edema in children should be kept in mind. Children with acute renal failure can present with edema due to renal retention of sodium and water. The nephrotic syndrome is one of the most common causes of generalized edema in childhood.

The classic findings of this disorder include marked proteinuria, hypoalbuminemia, and hyperlipidemia, along with generalized edema. We also tried to exclude the causes leading to both primary and secondary lymphedema. On the basis of the laboratory values and clinics of the patient, the team monitoring her decided that the lymphedema could be associated with her sirolimus therapy.

Sirolimus is a macrolide-group antibiotic that is isolated from *Streptomyces hygroscopicus* (4). Its use in preventing acute rejection after renal transplantations and in chronic allograft nephropathy is becoming increasingly common. The most frequent side effects are hyperlipidemia, thrombocytopenia, mild anemia, diarrhea, lymphocele, increase in the prevalence of inguinal herniation, and delay in wound healing (2). An increase in liver enzymes, development of acnes, interstitial pneumonia, thrombotic microangiopathy, angioedema, and eyelid edema has been reported in rare cases (5). The development of lymphedema secondary to sirolimus is a rare atypical complication of this treatment. Although its etiology is not fully understood, it is thought to be associated with prostaglandin synthesis stimulation in the endothelial cells, which is caused by sirolimus and results in increased permeability and lymphatic leakage in vascular segments as well as increased interstitial pressure and compression of the lymphatic ducts or impaired lymph drainage mechanism (4). mTOR is a downstream signal in the vascular endothelial growth factor (VEGF) C/D pathway, and mTOR inhibitors such as sirolimus are capable of inhibiting lymphangiogenesis in vitro. Sirolimus potentially inhibits VEGF C-driven proliferation and migration of lymphatic endothelial cells, and therefore, could be implicated in lymphatic reconstitution postsurgery (1). Sirolimus decreases regenerative and neoplastic lymphangiogenesis by inhibiting lymphatic endothelial cells. In rapamycin-treated animals, the anti-lymphangiogenic effect during tissue regeneration occurs with prolonged lymphedema, emphasizing the clinical relevance of this effect of mTOR inhibition in transplant recipients (6). However, it seems difficult to provide an evidenced model of pathogenesis to clarify the relationship between sirolimus and lymphedema. Probably for this reason, different responses to treatment are observed and discontinuation of the sirolimus therapy alone does not suffice as the treatment for lymphedema, as in our patient.

The prognosis of short bowel syndrome is being reversed significantly with the developments in total parenteral feeding. Bowel transplantation in such patients considerably improves the progress of the disease and quality of life. Till date, MSC transplantations have been attempted in animal models; clinical trials on humans are limited and are associated with liver failure, end-stage kidney failure, and congenital metabolic disorder (7). The patient in this report underwent ileum and colon resection because of injuries to the superior mesenteric artery, ileum, and colon she had developed after a firearm wounding; 4 months after the injury, she developed short bowel syndrome and underwent ileum transplantation from a cadaver and MSC transplantation to prevent rejection. This procedure was performed for the first time worldwide. The patient did not have any rejection attack following the transplantation and MSCs therapy. Consid-

ering its immune modulator effect, MSC transplantation is being used in patients with autoimmune and neurodegenerative diseases (7). It is also thought to be effective in the prevention and treatment of graft-versus-host disease. De Bartolomeis et al. (4) have reported a case where the patient received sirolimus immunosuppressive therapy following renal transplantation and had bilateral lower extremity edema, acid, and dyspnea complaints at postoperative month 3. In this case, the result of the sequential parasynthesis for exploring the tumoral and infectious cause was negative, and after discontinuation of sirolimus therapy, lymphedema was reversed completely. Castro et al. (8) reported the presence of lymphocele and cheilosis acid in abdomen following sirolimus therapy after renal transplantation and stated that there was no recurrence with a low-fat diet.

Aboujaoude et al. (9) reported that in three patients receiving sirolimus after renal transplantation, swelling and rash developed in the bilateral lower extremities, unilateral upper extremities, and breasts in postoperative weeks 11, 14, and 25. Lymphedema regressed in all patients after stopping sirolimus. In the meta-analysis published by Desai et al. (1) that involved 8 cases, they reported lymphedema in the bilateral lower extremity, upper extremity, genital region, and breast, which were associated with the use of sirolimus in various doses and for various periods. The common characteristic of the patients was that none of them had any family history. Damasiewicz et al. (10) reported a swelling in the left arm that developed in the 2<sup>nd</sup> week after a fly bite in a patient receiving sirolimus therapy for recurrent non-melanomatous skin cancer who had a history of renal transplantation. The scintigraphy applied to this patient indicated lymphatic obstruction in the left arm and sirolimus therapy was stopped; there was regression in the swelling after 4 weeks and complete recovery after 6 months. Al-Otaibi et al. (11) reported four cases that had a renal transplantation history associated with chronic glomerulonephritis and diabetic nephropathy and developed lymphedema in the extremities 7 to 30 months after sirolimus therapy. In these patients, there was a serious regression in lymphedema a few months after stopping sirolimus therapy. However, in our patient, lymphedema did not disappear although sirolimus therapy was discontinued. In cases where the discontinuation of sirolimus therapy is not useful, physical therapy and a rehabilitation program suitable for the patient must be initiated.

When we went through the literature, we found that 20 patients who received sirolimus therapy after they underwent renal or hepatic transplantation for various reasons developed lymphedema. In connection with this, 11 to 130 weeks after the initiation of treatment, their dose ranged between 2 and 10 mg/day; 13 patients had recovered from 4 weeks up to 6 years after stopping the medication and there was no change in seven patients (2,18). No difference was observed in the patients in terms of gender, and nearly all of them were middle-aged. Being a minor, our patient was different in this respect.

As for lymphedema development sites, single extremity and bilateral as well as lower/upper extremities have been reported in the literature; however, the involvement of three extremities as in our case is not very common. A general suggestion for treatment is to discontinue the medication. The case reports in

the literature indicate that stopping sirolimus therapy is sufficient for treating lymphedema, which was not the case in our patient. Because the follow-ups or long-term results of the cases in the literature are not available, it remains unknown whether discontinuation of sirolimus therapy is sufficient on its own or the disease relapses in such patients. There is no information in the literature about the rehabilitation of lymphedema in the patients reported, except in one case (12). This may be because they did not consider physical therapy and a rehabilitation approach or it is just not mentioned in these case reports. Therefore, our case report may help raise awareness among health professionals about rehabilitation. It is not possible to comment on the prognosis in the light of case reports, but considering other factors affecting prognosis and the treatments administered may be beneficial for us in clinical practice.

## Conclusion

In the light of this, it should be borne in mind that sirolimus may play a role in the etiology of lymphedema that develops in patients who have undergone transplantation and that cannot be explained. To prevent the development of a serious disability in such patients, early discontinuation of the medication should be considered. This type of patients should be directed to the rehabilitation clinic at an early stage for improving the patient's quality of life. Considering the ages and diagnoses of these patients and their difficult treatment processes, success in treatment becomes more important. Our case involving a patient with lymphedema associated with sirolimus therapy is important because of her significant recovery after the administration of complex decongestive therapy at our rehabilitation clinic. It is the first case in the literature involving MSC transplantation together with ileum transplantation; it is also noteworthy in terms of complex decongestive lymphedema treatment administered and the involvement of three extremities. As similar case reports will increase in the literature in the future, it will be easier to determine the method of making a treatment plan.

**Informed Consent:** The patient was informed about the presentation and signed informed consents was obtained.

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