Everolimus-Induced Systemic Serositis After Simultaneous Liver and Kidney Transplantation: A Case Report

K. Kim[a], D.W. Jeong[a], Y.H. Lee[a], Y.G. Kim[a], J.-Y. Moon[a], K.-H. Jeong[a], T.W. Lee[a], C.-G. Ihm[a], S.-H. Joo[b], H.-C. Park[b], and S.-H. Lee[a,*]

[a]Division of Nephrology, Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea; and [b]Department of Surgery, College of Medicine, Kyung Hee University, Seoul, Korea

ABSTRACT

Although everolimus, a mammalian target of rapamycin inhibitor, has been used as a potent immunosuppressive agent in organ transplantation, data regarding its adverse effect profile compared with that of sirolimus in clinical circumstances are limited. A 50-year-old man who underwent simultaneous liver and kidney transplantation 14 months previously was admitted with large pleural effusion, pericardial effusion, and ascites. Laboratory findings and cultures for possible infectious causes were all negative. Pericardial window surgery with drainage of the pericardial fluid was performed on day 3. Pleural and pericardial biopsy revealed nonspecific inflammation without evidence of malignant cells. Everolimus was discontinued and replaced by mycophenolate mofetil on day 4. Significant clinical improvement was observed after discontinuation of everolimus, and follow-up echocardiography and chest radiography showed no recurrence of the pericardial or pleural effusion after discharge.

MAMMALIAN target of rapamycin (mTOR) inhibitors, including sirolimus and everolimus, are macrocyclic antibiotics that have immunosuppressive and anti-proliferative activity and are used as potent immunosuppressants in organ transplantation. Concerns regarding the nephrotoxicity of calcineurin inhibitors (CNI) and the anti-tumoral effect of mTOR inhibitors have facilitated the development of CNI-sparing or withdrawal regimens with mTOR inhibitors in maintenance immunotherapy after kidney transplantation [1–4]. Everolimus is the hydroxyethyl derivative of sirolimus and has a similar chemical structure and mechanism of action but different pharmacokinetics and pharmacodynamics. The adverse effects reported for everolimus are largely similar to those of sirolimus. Pericardial and pleural effusions were reported to be rare adverse effects of sirolimus. However, only one case of pericardial effusion and no cases of multiple visceral effusions in patients treated with everolimus have been reported. We report the case of a patient who had systemic serositis with pericardial effusion, pleural effusion, and ascites, which were attributed to the administration of everolimus.

Case Report

A 50-year-old man with a history of liver and kidney transplantation presented with exertional dyspnea that began 1 month before his presentation at our transplantation center. He had received combined liver and kidney transplant from a deceased donor 14 months previously because of end-stage renal disease (ESRD) and decompensated alcoholic liver cirrhosis. The cause of the ESRD was diabetic nephropathy. Although the patient had a history of delayed graft function shortly after surgery and had been treated for acute cellular rejection with steroid pulse therapy 5 months after transplantation, kidney graft function was stable during the follow-up period (estimated glomerular filtration rate [eGFR], 50–60 mL/min/1.73 m^2).

Triple immunosuppressive therapy, including tacrolimus, mycophenolate mofetil, and prednisolone, was administered for 6 months after transplantation. However, mycophenolate mofetil was discontinued because of the development of leukopenia and everolimus was added to the maintenance immunosuppressive therapy. On admission, triple immunosuppressive therapy with tacrolimus, everolimus, and prednisolone had been maintained for 8 months.

*Address correspondence to Sang-Ho Lee, Department of Nephrology, Kyung Hee University Hospital at Gangdong, College of Medicine, Kyung Hee University, Sangil-dong 149, Gangdong-gu, Seoul 134-727, Korea. E-mail: lshkidney@khu.ac.kr

230 Park Avenue, New York, NY 10169

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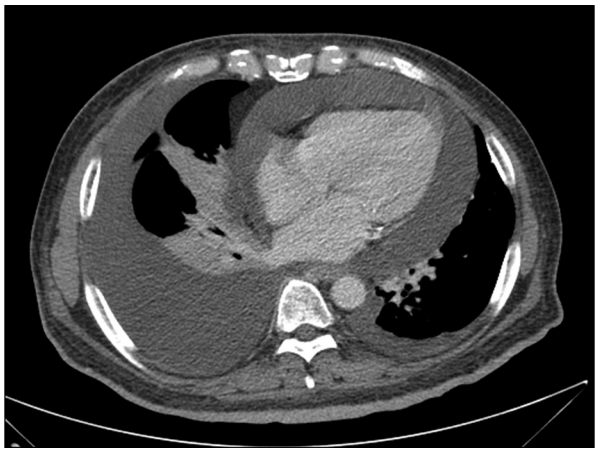

Fig 1. Computed tomography scan shows a large right-sided pleural effusion and pericardial effusion.

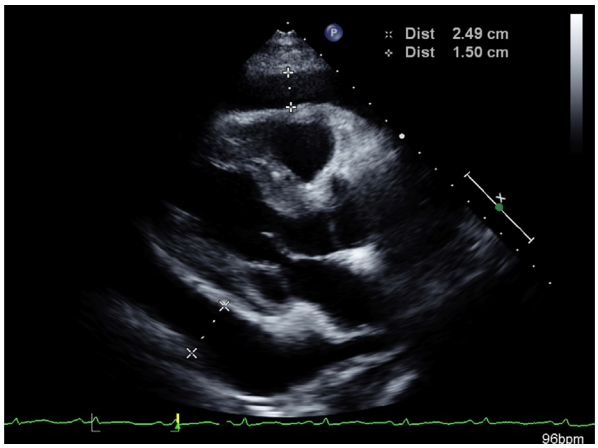

Fig 2. Echocardiography shows a large pericardial effusion with signs of impending cardiac tamponade.

Physical examination at the time of admission revealed moderate bilateral pretibial pitting edema and abdominal distension. Large right-sided pleural effusion and cardiomegaly were noted on chest radiography. Sinus tachycardia (heart rate of 105 beats per minute) with low-voltage QRS complexes and no ST-segment change were found on the electrocardiogram.

Initial laboratory findings included white blood cell count, 4370 /mm^3; C-reactive protein level, 1.0 mg/dL; hemoglobin concentration, 10.7 g/dL; serum creatinine level, 1.5 mg/dL; and spot urine protein-to-creatinine ratio, 2.07. The trough concentration of everolimus was 4.7 ng/mL. Chest and abdominal computed tomography revealed bilateral pleural effusion (larger on the right), large amounts of ascites, and pericardial effusion with no evidence of malignancy (Fig 1). The pleural fluid was an exudate (protein, 3.7 g/dL; glucose, 109 mg/dL; and adenosine deaminase level, 9.9 IU/L) with no malignant cells after diagnostic thoracentesis and tested negative for acid-fast bacilli staining and polymerase chain reaction for *Mycobacterium tuberculosis* (TB-PCR). Paracentesis showed exudative ascitic fluid (protein concentration, 4.1 g/dL; glucose level, 113 mg/dL; and albumin level, 2.5 g/dL). Polymerase chain reaction and antigen test results for cytomegalovirus were negative for the serum sample. Polymerase chain reaction for *Pneumocystis jirovecii* and the aspergillus antigen test also had negative results for the serum sample. Blood, urine, sputum, and pleural and ascitic fluid samples showed negative results for bacterial and fungal cultures. Transthoracic echocardiography showed large pericardial effusion with signs of impending cardiac tamponade and normal left ventricular systolic function (left ventricular ejection fraction, 67%) (Fig 2).

The patient underwent thoracoscopic pericardial window surgery on day 3 for the diagnosis and treatment of pericardial effusion. Drainage of the pericardial fluid and pericardial biopsy were performed during surgery. The pericardial fluid was exudative without any malignant cells (protein concentration, 4.7 g/dL; glucose level, 94 mg/dL; red blood cell count, 70,000/mm^2, and white blood cell count, 50/mm^2). Pericardial fluid samples for culturing bacteria, fungi, and *Mycobacterium tuberculosis* and TB-PCR all tested negative.

During the window operation, 400 mL of serous pericardial fluid was removed.

Pathological findings from the pericardial and pleural biopsy revealed non-specific inflammation with fibrosis and hemorrhage (Fig 3A,B).

Everolimus was discontinued 7 days after admission, and subsequent chest radiographs showed gradual improvement of the pleural effusion and cardiomegaly. Although a low dose of mycophenolate mofetil (720 mg/day) was added to the immunosuppressive regimen, a white blood cell count $>$4000/mm^3 was maintained thereafter.

The patient was discharged 17 days after admission. The dyspnea, peripheral edema, and abdominal distension improved at discharge. One month later, no pericardial effusion was apparent on follow-up echocardiography, and only a small right-sided pleural effusion was noted on chest radiography. The patient continued receiving immunosuppressive agents including tacrolimus, prednisolone, and low-dose mycophenolate mofetil, without the recurrence of pericardial effusion, pleural effusion, or peripheral edema. Serum creatinine level remained stable (eGFR $\geq$60 mL/min/1.73 m^2) during the follow-up period.

DISCUSSION

Although there has been significant improvement in early graft survival after renal transplant over the past two decades, long-term graft survival remains a challenge in renal transplantation. Various immunosuppressive protocols have been studied to improve long-term graft survival. Among them, mTOR inhibitors have been studied in CNI withdrawal protocols to reduce CNI-related nephrotoxicity. Several studies have shown that the conversion from a CNI to mTOR inhibitor is associated with better renal function