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CASE REPORT

Sirolimus therapy may cause cardiac tamponade

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The authors declare no conflict of interest.

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Summary

The side-effects associated with the immunosuppressive drug sirolimus are numerous and constitute a major limitation for its use in renal transplantation. In this study, we describe two cases of renal transplant recipients treated with sirolimus who developed pericardial tamponade associated with interstitial pneumonia, proteinuria, microcytic anemia and, in one case, lymphocytic meningitidis. An extensive search for infectious agents was negative, and all symptoms disappeared after sirolimus interruption. Therefore, this case demonstrates for the first time that sirolimus can cause pericardial tamponade as well as lymphocytic meningitidis.

Background

One important limitation of sirolimus use is its side-effects [1,2]. Here, for the first time, we describe two cases of cardiac tamponade caused by sirolimus therapy in renal transplant recipients (RTR), occurring at least 5 years after the introduction of the drug.

Case 1

A 67-year-old man with endstage renal disease related to nephroangiosclerosis received a deceased-donor kidney allograft in August 2005.

The immunosuppressive regimen was based on an induction with a humanized anti-IL2 receptor monoclonal antibody combined with mycophenolate mofetil, corticosteroids, and cyclosporine. The patient was randomized at week 12 to receive sirolimus.

Between November 2005 and April 2011, there was no event, except for a mild proteinuria (1 g/24 h) that was controlled with an angiotensin-converting enzyme (ACE) inhibitor. Serum creatinine varied between 100 and 120 μmol/l, and sirolimus was well tolerated.

In April 2011, the patient was admitted to the hospital for severe deterioration of clinical status associated with weight loss, fever, night sweats, persistent cough, and shortness of breath lasting for 1 month.

Upon admission, bilateral crackles were heard on the base of the lung fields. A cardiac exam identified a jugular venous distension. There was no peripheral edema.

The sirolimus dose was stable (4 mg/day), and the latest level on September 2010 was 10.3 ng/ml.

The white blood cell count was 6500/mm^3, with 64% neutrophils, 21% lymphocytes, and 10% monocytes. Hemoglobinemia was 10.3 g/dl with microcytosis (mean corpuscular volume of 66 μm^3), and the platelet count was 245 000/mm^3. The serum creatinine was 98 μmol/l, and the proteinuria/creatininuria ratio was 170 mg/mmol. C-reactive protein was 125 mg/l.

A chest computed tomography (CT) scanner showed bilateral interstitial pneumonia and an abundant and circumferential pericardial effusion (Fig. 1). A cardiac

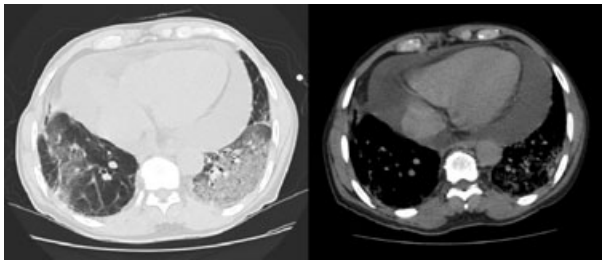

Figure 1 Chest computed tomography (CT) scan. A chest CT scanner showed bilateral interstitial pneumonia and an abundant and circumferential pericardial effusion.

echocardiogram confirmed the diagnosis of large pericardial effusion.

A bronchoalveolar lavage retrieved an exsudate with lymphocytosis (1100/mm^3 cellularity; 78% lymphocytes, 19% macrophages, and 5% neutrophils). The direct exam was negative for mycobacteria, pneumocystis, and yeast). Tests for legionella and pneumococcal antigenuria were both negative.

The patient was treated with third-generation cephalosporin and macrolides. Two days later, the C-reactive protein concentration rose to 180 mg/l. Sirolimus was stopped and replaced with tacrolimus.

Hemodynamic instability led a surgical pericardiocentesis. Lemon-colored fluid (1100 ml) was removed, and a catheter was left in place for 3 days. The pericardial fluid was exudative (protein concentration of 42 g/l) and did not contain white blood cells. The pericardial fluid and biopsy culture were negative for mycobacteria after 90 days. Polymerase chain reaction (PCR) tests for mycobacteria, Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and herpes simplex viruses (HSV) in the pericardial fluid and biopsy were negative. Blood and urine cultures were also negative.

One month later, the patient's clinical status was normal. An echocardiogram did not detect any pericardial effusion. C-reactive protein was 6 mg/l and hemoglobin was 14.8 g/dl, with a normalized mean corpuscular volume (80 μm^3). The serum creatinine concentration was 103 μmol/l, and the proteinuria/creatininuria ratio was 50 mg/mmol.

Case 2

A 64-year-old woman with endstage renal disease related to a tubulointerstitial nephropathy received a deceased-donor kidney in December 2006.

The immunosuppressive regimen was based on an induction therapy with humanized anti-IL2 receptor monoclonal antibody combined with mycophenolate mofetil administration, corticosteroids and cyclosporine. As the patient was part of a clinical trial, she also received reparixin, a specific inhibitor of the chemokine CXCL8.

A protocol graft biopsy performed at 3 months showed histological signs of calcineurin inhibitors nephrotoxicity, and cyclosporine was replaced by sirolimus.

No remarkable events were noticed during the follow-up of the patient, except for mild proteinuria (1 g/24 h), which was controlled with an ACE inhibitor, and microcytic anemia (mean corpuscular volume: 74 μm^3). The residual blood levels of sirolimus were between 8 and 12 ng/ml.

On August 2011, the patient was admitted to the hospital with a deterioration of her clinical status. Upon admission, the patient was febrile (39°C), crackles were heard on the base of the lung fields, and pitting peripheral edema without jugular venous distention was perceived.

The white blood cell count was 11 400/mm^3, with 94% neutrophils, 4% lymphocytes, and 1% monocytes; the hemoglobin concentration was 10.3 g/dl with microcytosis (mean corpuscular volume: 72 μm^3). The platelet count was 293 000/mm^3, serum creatinine was 262 μmol/l, and the proteinuria/creatininuria ratio was 370 mg/mmol. C-reactive protein concentration was 80 mg/l.

Chest radiography and CT scan showed bilateral interstitial pneumonia and a large pericardial effusion. Sirolimus was stopped because of possible side-effects, and cyclosporine was introduced, along with third-generation cephalosporin and macrolides.

Twenty-four hours later, the patient remained febrile. A physical exam showed shortness of breath, requiring nasal oxygenotherapy (6 l/min), and confusion.

A cardiac echocardiogram showed a large pericardial effusion with hemodynamic compromise. A surgical pericardiocentesis obtained 650 ml of lemon-colored fluid without leukocytes and abnormal cells. Pericardial fluid and biopsy culture were both negative for bacteria; culture for mycobacteria was negative after 90 days. PCR tests for mycobacteria, CMV, EBV, and HSV were negative for the pericardial fluid and biopsy. A histological analysis of the pericardial biopsy did not reveal any granuloma or fungic elements. Blood and urine cultures were also negative.

The brain CT scan was normal. A lymphocytic meningitis was diagnosed on the cerebrospinal fluid analysis. The direct exam and bacterial cultures were negative, as well as PCR for HSV, CMV, and EBV.

A bronchoalveolar lavage retrieved an inflammatory fluid with a majority of neutrophils. No microorganism (bacteria, mycobacteria, yeast, and parasite) was detected. The culture test for mycobacteria was negative after 90 days.

The antibiotherapy was enlarged for tazobactam-piperacillin, fluoroquinolone, amoxicillin and gentamicin with the addition of aciclovir. The trachea was canulated 2 days later because of the alteration of the gaseous exchanges. Continuous veno-venous hemodiafiltration was necessary for 4 days because of an acute renal failure. The patient was extubated 2 weeks later.

The antibiotic and antiviral therapies were stopped 5 days after their introduction because of a lack of efficacy. Rifampicin, isoniazide, ethambutol, and pyrazimanide were introduced and stopped 2 weeks later because of negative tests for mycobacteria.

THPHA/VDRL and tests for clamydia trachomatis and pneumoniae, mycoplasma pneumoniae, rickettsia, coxiella burnetii, bartonella, Lyme disease, and brucella serologies were negative. PCR tests for Human Herpes viruses 6 and 8 (HHV6 and 8), parvovirus B19 and HSV in the blood were also negative. Blood samples tested positive for EBV by PCR (4.1 log).

Three weeks after the initial admission, the clinical status of the patient dramatically improved, with a normal physical exam. The inflammatory biologic syndrome disappeared, and radiological signs of pneumonia and pericardiac effusion disappeared. Hemoglobinemia was 12.3 g/dl, with a normalized mean corpuscular volume (85 μm^3). Serum creatinine concentration was 140 μmol/l, and the proteinuria/creatininuria ratio was 50 mg/mmol.

Discussion

Pericardial effusion is rarely observed in renal transplant recipients. The overall incidence of pericarditis and/or pericardial effusion was 2.4% [3] in a series of 1497 patients, followed during a 2-month period, and the majority of the etiologies were uremia and CMV. In the cases reported here, there was no evidence of uremia or CMV disease. Cases of cardiac tamponade have rarely been reported in renal transplant recipients, and very little is known about their etiologies [4,5].

The Wyeth's safety database of pericardial effusion coincident with sirolimus therapy in solid organ transplant populations [6] reports that the highest rate of pericardial effusion is observed after cardiac transplantation, with a pericardial effusion prevalence of 28,6% and a cardiac tamponade prevalence of 6,6%. In RTR, the prevalence of pericardial effusion ranged from 0.7% to 1.9% after 3 years of follow-up, and 50% of the pericardial effusions required surgical intervention. Notably, these associations do not imply a causal link between SRL use and tamponade.

Pericardial effusions are rarely observed in other transplant patients under sirolimus therapy; the prevalence rate was 2.9% in liver transplant recipients [7]. Cardiac tamponade has been anecdotically reported in a child with a cardiac allograft [5] and in a patient who received a bone marrow transplant for an advanced myelodysplastic syndrome [8]. The mechanisms of cardiac tamponade related to sirolimus use are unknown, and a proinflammatory mechanism, similar to that which is the cause of pneumonitis, is likely. Indeed, the association of inflammatory anemia and pneumonitis may suggest an inflammatory origin. We excluded most of the potential causes of pericardial effusion, including infections and neoplasms. Moreover, there was no evidence for the nephrotic syndrome, which is rarely seen under sirolimus therapy. The proteinuria was less than 1g/day, albuminemia within the normal range, and there was no systemic edema.

The cases we have reported here strongly suggest that sirolimus can cause cardiac tamponade at least 5 years after the introduction of the therapy:

1. An extensive search for infectious causes (viral, bacterial, including tuberculosis, and fungi) was undertaken, and these tests were negative in the pericardial and pleural fluid and in pericardial biopsies.

2. Many typical side-effects of sirolimus were associated with pericardial tamponade, including noninfectious interstitial pneumonia, chronic microcytic anemia, and proteinuria, which can all be caused by sirolimus [9,10].

3. All of these effects were resolved after sirolimus discontinuation.

Aseptic lymphocytic meningitidis has never been associated with sirolimus in the literature. However, cerebrospinal fluid was never analyzed in renal transplant recipients treated with sirolimus in the context of drug-associated adverse effects.

In conclusion, we have described two cases that strongly support the role of sirolimus therapy in the development of cardiac tamponade in RTR. Sirolimus therapy should be stopped early or switched in an RTR presenting with clinical or radiological signs of cardiac tamponade or pericardial effusion because of the potential life-threatening risk.

Authors contribution

DB and NP: wrote the paper. GD, AS, AD, MFM, DA and ChL: took care of the patients.

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