Pericardial Effusion Associated With Sirolimus Use After Renal Transplantation: A Single-Center Case Series

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ABSTRACT

Pericardial effusion and cardiac tamponade following renal transplantation have been recognized as a potentially serious complications associated with the use of sirolimus for immunosuppression. Our study aims to analyze the development of sirolimus-associated pericardial effusion.

Patients who underwent renal transplantation at our institution between 2001 and 2014 were reviewed and the correlation between sirolimus exposure and pericardial effusion was determined. Nineteen out of 792 patients who received a renal transplant over this 14-year period (incidence 2.4%) developed symptomatic pericardial effusion (determined by the need for pericardiocentesis or a pericardial window). All patients had a pre-transplantation cardiac workup, including echocardiogram, which did not reveal the presence of pericardial effusion. Our cohort of patients is mostly male (57.9%) and Caucasian (73.7%), which is consistent with the makeup of transplant recipients at our center. The mean age was 52.42 years at the time of transplantation. The development of symptomatic pericardial effusions occurred at a mean of 5.06 (.5–9.8) years after renal transplant while on sirolimus therapy. Sirolimus levels at diagnosis were 5.19–7.47 ng/mL. No significant pericardial effusion (resulting in tamponade physiology) recurred after therapeutic intervention, including cessation of sirolimus with or without pericardial drainage. This study is the largest single-center report of the possible association between pericardial effusion in renal transplant recipients who received sirolimus. Due to the widespread use of sirolimus in organ transplantation, clinicians must remain vigilant for this potential cardiac complication.

AN important consideration in selecting an immunosuppressive regimen is balancing efficacy with side effects and complications. Sirolimus, isolated in 1972 from the bacterium *Streptomyces hygroscopicus*, was approved for use in transplant recipients in 1999 for both kidney and liver transplantation. Sirolimus is an inhibitor of cytokine-receptor signal transduction resulting in impaired T-cell proliferation [1,2]. Mechanistically similar to tacrolimus, sirolimus binds to a family of immunophilins called FK-binding protein 12 (FKBP12), and instead of targeting calcineurin the sirolimus-FKBP12 complex targets and inhibits the mammalian target of rapamycin (mTOR). mTOR inhibition leads to decreased interleukin 2 signal transduction to induce cell cycle arrest in G1- to S-phase [3]. One of the advantages of sirolimus is its decreased long-term nephrotoxicity compared to calcineurin inhibitors resulting in improved long-term glomerular filtration rate [4,5]. Interestingly, sirolimus has both innate antiviral and antineoplastic properties [6,7]. The antineoplastic effects of

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sirolimus were demonstrated in 2 studies that showed decreased incidence of dermal Kaposi's sarcoma in renal transplant patients and remission of AKT (+) lymphoma in mice when combined with doxorubicin [8,9]. Liacini et al also found sirolimus and leflunomide combination therapy to be effective for post-transplant BK viral infection through protein kinase pathway inhibition [10]. These characteristics make sirolimus an attractive alternative for long-term immunosuppression. However, toxicity associated with sirolimus spans multiple systems: peripheral edema (20%-58%), hypertension (49%), deep vein thrombosis, pulmonary embolism, hypertriglyceridemia (45%-57%), anemia (23%-33%), thrombocytopenia (14%-30%), leukopenia, lymphocele, cytomegalovirus, and Epstein-Barr infection, focal segmental glomerulosclerosis, hepatotoxicity, interstitial pneumonitis, pulmonary fibrosis, pleural effusion, and lymphedema with ascites [2,11,12]. Recently, pericardial effusion with or without associated tamponade physiology has been described as a potential complication of sirolimus use. However, there is a paucity of data on this condition, despite the associated potential for mortality and morbidity. In this study, we present a single-center case series, the largest to date, from our institution, focusing on 19 renal transplant recipients who were all treated with combination immunosuppression including sirolimus (from 792 total patients) who developed symptomatic pericardial effusions with and without tamponade physiology. Our center has one of the richest experiences in the use of sirolimus as part of a long-term immunosuppression regimen [13]. We analyzed demographic and outcome parameters to determine the incidence of pericardial effusion post-transplant. Because symptomatic pericardial effusions can present as life-threatening late complications associated with sirolimus use in renal transplant patients, we aim to highlight our experience.

MATERIALS AND METHODS

We retrospectively reviewed the electronic medical record database at our institution, focusing on all renal transplant recipients who received sirolimus between January 2001 and December 2014 as part of their maintenance immunosuppression regimen. In our institution, all patients receive a standard post-transplant regimen that includes thymoglobulin (4–5 mg/kg) for induction, and are subsequently placed on a combination of tacrolimus, sirolimus, and mycophenolate mofetil (MMF) for maintenance immunotherapy (see Table 1, reprinted with permission from [13]). Per our protocol, sirolimus is introduced on post-transplant day 7 without a loading dose. Serum sirolimus concentrations were maintained at 4–6 ng/mL in the first 3 months and 6–9 ng/mL at 3 months and after, with parallel minimization of tacrolimus dosing (Table 1).

A total of 31 patients were identified through our electronic medical record system by searching for a diagnosis of renal transplant and pericardial effusion or cardiac tamponade. Out of those 31 patients, 19 met our inclusion criteria, which were 1. renal transplant patients with a functioning graft at the time of diagnosis of pericardial effusion; and 2. on sirolimus post-transplant and at the time of diagnosis, and development of symptomatic pericardial effusion with or without tamponade physiology. Patient records were carefully reviewed to extract relevant demographic data, time period from transplant to development of pericardial effusion, treatment received, range of sirolimus levels at the time of diagnosis, clinical characteristics (other immunosuppression medications, comorbidities, cause of end-stage renal disease), and outcomes of intervention. Patients with pericardial effusion and co-morbid conditions such as lymphoma, graft failure, and previous coronary artery disease needing cardiac interventions were excluded from our analysis.

Table 1. Immunosupression Protocol

Induction	
Thymoglobulin	.5–1.0 mg/kg/d for a total dose of 4–5 mg/kg*
Solumedrol	Day 0, 375 mg; Day 1, 200 mg; Day 2, 160 mg; Day 3, 120 mg; Day 4, 80 mg; Day 5, 40 mg; Day 6, 20 mg
Tacrolimus	8–10 ng/mL on discharge†
Mycophenolate Mofetil	Days 0–5, 2 g/d; Day 6, 1 g/d
Sirolimus	Day 6, 8–10 ng/mL‡
Maintenance	
Tacrolimus	Day 90 (discharge), 8–10 ng/mL, then 2 ng/mL†
Mycophenolate Mofetil	1 g/d
Sirolimus	8–10 ng/mL‡

*Dose reduced secondary to thrombocytopenia/leukopenia.
†12-hour trough.
‡24-hour trough.

All patients diagnosed with pericardial effusion were assessed with transthoracic echocardiograms performed by experienced technicians. Studies were read by experienced cardiologists at our institution. Based on transthoracic echocardiogram, pericardial effusion was graded as small (less than 1 cm in dimension), moderate (1–2 cm), or large (>2 cm) effusions.

The protocol of this study was approved by our institutional review board.

RESULTS

Demography of Patients Who Developed Symptomatic Pericardial Effusions While on Sirolimus

A total of 792 renal transplants were performed at Albany Medical Center between 2001 and 2014, and 19 patients with a functioning graft at the time of this study (incidence 2.4%) were found to have a symptomatic pericardial effusion while being maintained on sirolimus as part of their immunosuppression regimen. Table 2 illustrates the demographic characteristics of the study population. The median age at time of transplantation was 52.31 years old. Patients were predominantly male (57.9%) and Caucasian (73.7%). Most of the patients received deceased donor renal transplants (89.5%), with primary cause of end-stage renal disease being diabetes and/or hypertension. Patients underwent an extensive pre-transplant cardiac workup including echocardiogram, electrocardiogram, and cardiac stress testing. We found that, pre-transplant, 47.38% of the study population had cardiac interventions (55.6% cardiac catheterization, 44.5% coronary artery bypass grafting, or stenting), but none had evidence of pericardial effusion.

Table 2. Patient Demographics

Age at Transplantation (y)	
Mean	52.32 ± 9.74
21–40	10.53%
41–60	73.68%
61–80	15.79%
Male/Female	57.89%/42.11%
Ethnicity	
Caucasian	73.68%
African-American	21.06%
Asian	0%
Hispanic	5.26%
BMI at time of effusion (mean ± SD)	27.19 ± 5.65
Never smoked/former smoker	26.32%/73.68%
Cause of ESRD	
PKD	26.32%
DM/HTN	36.84%
DM	10.53%
HTN	52.63%
LRT/DDRT	10.53%/89.47%
Cardiac Co-morbidities	
CABG/Coronary stent post-transplant	21.06%
PTCA Post-transplant	26.32%
Arrythmia	15.79%
CVA	5.25%
CHF	10.53%
MI	21.05%
Concomitant Immunosuppression	
Corticosteroids	15.79%
Prograf	94.74%
Myfortic (Novartis)	5.26%
Cyclosporine	5.26%
MMF	78.94%

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CVA cerebrovascular accident; DDRT, deceased donor renal transplant; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; LRT, living renal transplant; MI, myocardial infarction; MMF, mycophenolate mofetil; PKD, polycystic kidney disease; PTCA, percutaneous transluminal coronary stenting; SD, standard deviation.

Besides sirolimus, at the time of diagnosis, this patient cohort was maintained on tacrolimus (94.7%), MMF (78.9%), corticosteroids (15.8%), Myfortic (5.3%; Novartis, Basel, Switzerland), and cyclosporine (5.3%).

Development of Pericardial Effusion Post-Transplant

As described in Table 3, patients developed symptomatic pericardial effusions and/or tamponade physiology on average 5.06 ± 2.76 years after transplant. The mean sirolimus serum concentration at the time of diagnosis was 6.93 ± 1.94 ng/mL. There was no clear association between length of time following transplant and sirolimus levels in our cohort of patients (Fig 1). All 19 patients had symptomatic pericardial effusion, with 14 (73.7%) experiencing tamponade physiology on cardiac echocardiogram and 5 (26.3%) patients not doing so. A majority of patients were diagnosed with a "moderate" pericardial effusion (52.6%). At the time of diagnosis, patients had good to excellent renal function (average serum creatinine 1.79 ± 0.87 ng/dL). No evidence of infectious, autoimmune, or malignancy-related causes were identified in any of the patients included in our series, including microscopic and culture analysis of the drained effusion fluid. All patients were diagnosed through echocardiograms performed by experienced technicians and studies were read by experienced cardiologists at our institution. Eighteen of the 19 patients required interventions aimed at draining the pericardial fluid. Specifically, 17 of these 18 (89.5%) underwent pericardial window while 1 (5.3%) underwent pericardiocentesis. One symptomatic patient was treated only by discontinuing sirolimus, which resolved the effusion. Sirolimus was also stopped after the diagnosis of effusion in all patients, with no documented recurrence in any of the 19 patients.

Table 3. Clinical Characteristics of Patients With Pericardial Effusions

Time to Develop PE Post-transplant (y)	5.08 ± 2.76
Renal Function at Diagnosis	
Serum creatinine (mg/dL)	1.79 ± .87
eGFR	44 ± 22.05
Sirolimus concentration at diagnosis (ng/mL)	6.93 ± 1.94
Clinical diagnosis	
Pericarditis	10.53%
Cardiac tamponade	73.68%
Symptomatic PE without tamponade	26.32%
Size of Pericardial Effusion	
Large	36.84%
Moderate	52.63%
Small	10.52%
Therapeutic Intervention (+) Stopping Sirolimus	
Pericardial window	89.47%
Pericardiocentesis	5.26%
No drainage	5.26%

Size of pericardial effusions: small (<1 cm), moderate (1–2 cm), and large (>2 cm).
Abbreviations: eGFR, estimated glomerular filtration rate; PE, pericardial effusion.

DISCUSSION

Sirolimus remains a popular component of the immunosuppression armamentarium. Long-term renal function appears to be preserved when using a combination of calcineurin inhibitors, MMF, and sirolimus [13]. Therefore, although sirolimus use is not as widespread in renal transplant recipients as tacrolimus, MMF, and corticosteroids, it is an attractive alternative for minimizing steroid exposure with associated improvements in postoperative morbidities [13,14]. Sirolimus has also been shown to have antiviral/antineoplastic effects, which may be beneficial in some cases. However, a number of adverse effects have also been described, one of which is the development of symptomatic lymph accumulation (seen with both sirolimus and its derivative, everolimus), including lower-extremity edema, diffuse lymphedema, pleural and pericardial effusions, and ascites [15–19]. In most cases, resolution of lymphatic accumulation has been documented following cessation of sirolimus, indicating a possible direct relationship between sirolimus use and lymph accumulation.

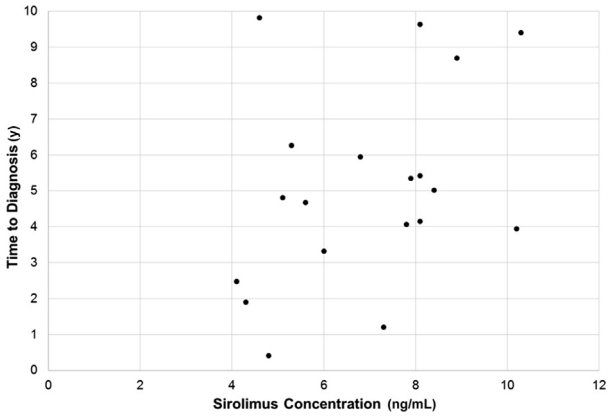

Fig 1. Association between sirolimus concentration and time to diagnosis of pericardial effusion. Nineteen patients developed symptomatic pericardial effusions following renal transplantation while on sirolimus. Development of symptomatic pericardial effusions occurred on average 5.06 years after transplant and with a serum sirolimus concentration of 6.93 ± 1.94 ng/mL. There was no clear association between receiving sirolimus, concentration of serum sirolimus, and development of pericardial effusion, although timing tended to appear later and in the setting of higher serum concentration.

As the most feared lymph-accumulating side effect seen with sirolimus, pericardial effusion has been shown to entail significant risks of morbidity and mortality. However, the specific mechanisms leading to the development of pericardial effusions are unclear. Lymphatic drainage has several critical components, including proliferation, maintenance, and migration, all of which are regulated by vascular endothelial growth factor. mTOR is found downstream in the vascular endothelial growth factor activation pathway and therefore inhibition of mTOR by sirolimus may suppress lymph-angiogenesis, leading to increased lymphatic drainage and impaired clearance [20]. The inhibition of lymph-angiogenesis could therefore lead to decreased lymph clearance and result in an accumulation of lymphatic fluid [15,21–25].

Most of the literature reporting on pericardial effusions associated with sirolimus use in solid organ transplantation have been case reports [12,26]. Most of the previously published data focused on heart [26–30] and liver transplant recipients [12,31]. In 2004, Montalbano et al described 4 cases of pericardial effusion in sirolimus-treated liver transplant recipients [12]. Three of these patients also had pleural effusions. In 2005, Truong et al published the first description of the occurrence of a pericardial effusion requiring pericardiocentesis in a sirolimus-treated pediatric kidney transplant recipient [32]. Rocha et al described a case of pericardial effusion 9-years post-renal transplantation with resolution after drainage and cessation of sirolimus [23]. In 2013, Bertrand et al reported on 2 cases of tamponade presenting 5 years after renal transplantation. In both cases, effusions resolved with a combination of pericardiocentesis and sirolimus cessation [33]. Everolimus was also found to be associated with recurrent pericardial effusions 4.5 years following renal transplantations [25]. These pericardial effusions were found to respond to the cessation of everolimus [25]. Finally, a larger series identified 56 cases (35 in kidney transplant recipients) of pericardial effusions coincident with sirolimus therapy. The diagnosis of pericardial effusion was found to be independent of other possible concomitant conditions such as cardiac trauma and viral or drug-induced pericarditis [26]. From these studies the reported incidence of pericardial effusion associated with sirolimus was determined to be between .7%-2.3%, with a median time to onset of 38 weeks (range, 3–202 weeks). However, there were no differences in the incidence of pericardial effusion between patients treated de novo or patients switched to sirolimus post-transplant [26].

In our study, we describe 19 patients with symptomatic pericardial effusions not attributed to any other causal factor. The incidence among our patients was found to be 2.4%, but this probably under-represents the real incidence because we only captured symptomatic pericardial effusions. Twelve additional cases were reported, but potential confounding conditions such as lymphoma, graft failure, and pre-transplant coronary artery bypass grafting also existed in these cases so they were excluded from our review. In our patients, the average time to diagnosis was approximately 5 years, which was similar to reported timelines from other studies (4.5–9 years), suggesting a late onset [23,25,32,33]. Similarly, in all cases where sirolimus levels were reported, the trough level was 8–11 ng/mL [23,25,32,33]. Our data also showed that patients who developed pericardial effusions were mostly Caucasian men, individuals with a history of smoking, recipients of deceased-donor renal transplants, and obese, but these rates are consistent with our innate transplant recipient population, so we did not find strong demographic or cardiac-related diagnoses to indicate causality between these factors and risk for the development of pericardial effusions. In 18 of the 19 patients, the pericardial effusions resolved following drainage and withdrawal of sirolimus. It is possible that cessation of sirolimus alone may have allowed the effusions to resolve, but in several reports, pericardial effusions did not resolve or were found to recur after pericardiocentesis and only resolved following discontinuation of sirolimus. We therefore determined that maximal therapy (drainage and discontinuation of sirolimus) was the safest way to treat symptomatic pericardial effusions, and in fact we did not see recurrences in any patients following both drainage and cessation of sirolimus.

CONCLUSIONS

Given our rich experience with long-term sirolimus use, we are able to present the largest single center series of symptomatic pericardial effusions following renal transplantation. Our data suggests a slightly higher incidence than what has been described in the literature so far, although, based on specific inclusion and exclusion criteria, our study may fall short of representing the true incidence

(other co-morbid conditions, asymptomatic, etc.); the actual incidence may be higher. Further studies will help us determine specific risk factors associated with the development of symptomatic pericardial effusions in the setting of long-term sirolimus use. Vigilance and a high index of suspicion remain paramount to diagnose and treat this potentially life-threatening complication.

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REFERENCES

[1] Cravedi P, Ruggenenti P, Remuzzi G. Sirolimus for calcineurin inhibitors in organ transplantation: contra. Kidney Int 2010;78:1068–74.

[2] Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. Transplant Proc 2003;35:S7–14.

[3] Hardinger KL, Koch MJ, Brennan DC. Current and future immunosuppressive strategies in renal transplantation. Pharmacotherapy 2004;24:1159–76.

[4] Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. Lancet 2000;356:194–202.

[5] MacDonald AS. A worldwide, phase II, randomized, controlled, safety, and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 2001;71:271–80.

[6] Jouve T, Rostaing L, Malvezzi P. Place of mTOR inhibitors in management of BKV infection after kidney transplantation. J Nephropathol 2015;5:1–7.

[7] Easton JB, Houghton PJ. mTOR and cancer therapy. Oncogene 2006;25:6436–46.

[8] Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. New Engl J Med 2005;352:1317–23.

[9] Novak K. Means to an end. Nat Rev Cancer 2004;4. 332-332.

[10] Liacini A, Seamone ME, Muruve DA, Tibbles TA. Anti-BK virus mechanisms of sirolimus and leflunomide alone and in combination: toward a new therapy for BK virus infection. Transplantation 2010;90:1450–7.

[11] Stallone G, Infante B, Grandaliano G, Gesualdo L. Management of side effects of sirolimus therapy. Transplantation 2009;87:S23–6.

[12] Montalbano M, Neff GW, Yamashiki N, Meyer D, Bettiol M, Slapak-Green G, et al. A retrospective review of liver transplant patients treated with sirolimus from a single center: an analysis of sirolimus-related complications. Transplant J 2004;78:264–8.

[13] Lopez-Soler RI, Chan R, Martinolich J, Park L, Ata A, Chandolias N, et al. Early steroid withdrawal results in improved patient and graft survival and lower risk of post-transplant cardiovascular risk profiles: a single-center 10-year experience. Clin Transplant 2017;31. https://doi.org/10.1111/ctr.12878.

[14] Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, et al. OPTN/SRTR 2017 annual data report: kidney. Am J Transplant 2019;19:19–123.

[15] Castro G, Freitas C, Beirão I, Rocha G, Henriques AC, Cabrita A. Chylous ascites in a renal transplant recipient under sirolimus (rapamycin) treatment. Transplant Proc 2008;40:1756–8.

[16] Papali A, Giannetti N, Cantarovich M. Unilateral upper extremity edema associated with sirolimus in a heart transplant patient. Transplantation 2007;83:240.

[17] Aboujaoude W, Milgrom ML, Govani MV. Lymphedema associated with sirolimus in renal transplant recipients. Transplantation 2004;77:1094–6.

[18] Ibáñez JP, Monteverde ML, Goldberg J, Diaz MA, Turconi A. Sirolimus in pediatric renal transplantation. Transplant Proc 2005;37:682–4.

[19] Al-Otaibi T, Ahamed N, Nampoory MRN, Al-Kandari N, Nair P, Hallm MA, et al. Lymphedema: an unusual complication of sirolimus therapy. Transplant Proc 2007;39:1207–10.

[20] Kreuger J, Nilsson I, Kerjaschki D, Petrova T, Alitalo K, Claesson-Welsh L. Early lymph vessel development from embryonic stem cells. Arterioscler Thromb Vasc Biol 2006;26:1073–8.

[21] Martin y, Porras M, Waleffe A, Pierard L. Treatment of recurrent pericarditis: case report and review of literature [in French]. Rev Med Liege 2007;62:21–4.

[22] Palin NK, Savikko J, Koskinen PK. Sirolimus inhibits lymphangiogenesis in rat renal allografts, a novel mechanism to prevent chronic kidney allograft injury. Transpl Int 2012;26:195–205.

[23] Rocha S, Pedroso S, Almeida M, Dias L, Martins L, Henriques A, et al. Pericardial and pleural effusions associated with sirolimus and discussion of possible mechanisms. Port J Nephrol Hypert 2012;26:165–9.

[24] Keogh A, Richardson M, Ruygrok P, Spratt P, Galbraith A, O'Driscoll G, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years. Circulation 2004;110:2694–700.

[25] Zeidan S, Ribes D, Cointault O, Gautier M, Marcheix B, Kamar N. Everolimus-induced recurrent pericardial effusion after kidney transplantation. Transpl Int 2013;26:e36–7.

[26] Steele GH, Adamkovic AB, Demopoulos LA, Rothrock LC, Caulfield ME, Blum MD, et al. Pericardial effusion coincident with sirolimus therapy: a review of Wyeth's safety database. Transplantation 2008;85:645–7.

[27] Sagristà-Sauleda J, Mercé J, Permanyer-Miralda G, Soler-Soler J. Clinical clues to the causes of large pericardial effusions. Am J Med 2000;109:95–101.

[28] Hauptman PJ, Couper GS, Aranki SF, Kartashov A, Mudge GH, Loh E. Pericardial effusions after cardiac transplantation. J Am Coll Cardiol 1994;23:1625–9.

[29] Al-Dadah AS, Guthrie TJ, Pasque MK, Moon MR, Ewald GA, Moazami N. Clinical course and predictors of pericardial effusion following cardiac transplantation. Transplant Proc 2007;39:1589–92.

[30] Quin JA, Tauriainen MP, Huber LM, McIntire DD, Kaiser PA, Ring WS, et al. Predictors of pericardial effusion after orthotopic heart transplantation. J Thorac Cardiovasc Surg 2002;124:979–83.

[31] Holbro A, Ahmad I, Busque L, Cohen S, Lachance S, Roy DC, et al. Cardiac tamponade potentially related to sirolimus following cord blood transplantation. Bone Marrow Transplant 2011;47:294–5.

[32] Truong U, Moon-Grady AJ, Butani L. Cardiac tamponade in a pediatric renal transplant recipient on sirolimus therapy. Pediatr Transplant 2005;9:541–4.

[33] Bertrand D, Desbuissons G, Pallet N, Debure A, Sartorius A, Anglicheau D, et al. Sirolimus therapy may cause cardiac tamponade. Transpl Int 2012;26:e4–7.