A Pediatric Case of Sirolimus-Associated Pneumonitis After Kidney Transplantation

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Sirolimus is an immunosuppressive medication often used in solid organ transplantation. It has been associated with severe side effects, including pulmonary toxicity. In adult patients, a single center study found that 14% of those treated with sirolimus developed pulmonary pneumonitis; however, the incidence in the pediatric population is not known. Most reports in adult patients indicate that elevated drug concentrations and a prolonged duration of use are associated with pulmonary toxicity. We report a case of a 17-year-old male kidney transplant recipient who developed rapid-onset respiratory failure, necessitating mechanical ventilation and acute renal replacement therapy for ultrafiltration secondary to sirolimus-induced pneumonitis. He had been treated for acute rejection with corticosteroids 17 days prior to the development of pneumonitis. His symptoms developed within 1 week of initiation of sirolimus and with a serum concentration of 1.1 ng/mL. Sirolimus was discontinued, and, following aggressive diuresis and ventilatory support, his respiratory status returned to baseline. Sirolimus-induced pneumonitis is an important diagnosis to be considered in any transplant recipient receiving sirolimus with new onset fever, cough, or dyspnea without an identifiable source, especially if there is a preceding history of treatment with high-dose corticosteroids.

ABBREVIATIONS CMV, cytomegalovirus; IV, intravenously

KEYWORDS adverse drug reaction; kidney transplant; pediatrics; pneumonitis

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Introduction

Sirolimus is an inhibitor of mechanistic target of rapamycin complex 1 that halts T-lymphocyte proliferation.¹ It gained use in the 1990s as a less nephrotoxic alternative to calcineurin inhibitors.² However, sirolimus use can be associated with severe side effects.³ Amongst several proinflammatory side effects, pulmonary toxicity has been reported in solid organ transplant recipients.^{4–7} In adult patients, a single-center study found that 14% of those treated with sirolimus developed pulmonary pneumonitis.⁸ We present a case of sirolimus-induced interstitial pneumonitis in a pediatric kidney transplant recipient who had rapid-onset respiratory failure, pneumonitis, and non-cardiogenic pulmonary edema after sirolimus initiation.

Case

The patient is a 17-year-old male with a history of anterior urethral valves leading to end-stage kidney disease and had recently undergone his second kidney transplant. Six months after transplant, the patient was admitted due to fever and acute kidney injury. His induction immune suppression included thymoglobulin, basiliximab, corticosteroids, and rituximab and maintenance included long-acting tacrolimus (goal range 6–8

ng/mL) and mycophenolic acid that was switched to prednisone 10 mg daily due to profound leukopenia. For the fever, an infectious workup showed only low-grade cytomegalovirus (CMV) polymerase chain reaction positivity in serum (1541 copies/mL). He underwent renal biopsy for the acute kidney injury and was diagnosed with moderate acute T-cell mediated rejection 1A and 2A. Serum donor-specific antibodies were negative, and histopathological evaluation revealed positive anti-C4d antibody staining by immunofluorescence indicating an element of non-human leukocyte antigen antibody-mediated rejection. Intravenous immunoglobulin and pulse intravenous methylprednisolone (500 mg daily for 2 days with dose reduction of 50% every 2 days until reaching a dose of 60 mg daily) were given.

With this treatment the fever resolved, and his serum creatinine started trending down. In light of his recent rejection episode, we added sirolimus (Rapamune, Pfizer, Philadelphia, PA) 1 mg (0.01 mg/kg) 1 tablet daily to his immunosuppressive regimen prior to discharge; no loading dose was administered. The addition of sirolimus with a targeted concentration of 3 to 4 ng/mL was done with the plan to decrease the long-acting tacrolimus dose to achieve a lower goal concentration of 4 to 5 ng/mL. Following his discharge, his prednisone was tapered down to his former regimen of 10 mg daily

Table 1. Concomitant Medications With Days Since Initiation to Onset of Pneumonitis Symptoms Including Dose and Frequency of Medications

Medication	Days Since Initiation	Dose	Frequency
Amlodipine	88	5 mg	Twice daily
Candesartan	14	4 mg	Twice daily
Cephalexin	10	250 mg	Daily
Clonidine	3	0.2 mg	Daily
Hydroxychloroquine	150	200 mg	Daily
Multivitamin	Unknown, unchanged over 6 months		Daily
Prednisone	157	10 mg	Daily
Sirolimus	9	1 mg	Daily
Sodium bicarbonate	89	650 mg	Twice daily
Valganciclovir	10	450 mg	Daily
Tacrolimus	185	8 mg	Daily

and his tacrolimus dose was unchanged.

The concomitant medications are listed in Table 1. None of these medications are known to cause an interaction with sirolimus. He had a history of severe hypersensitivity reactions to a wide range of medications including penicillins and sulfonamides. Of note, no signs of hepatic dysfunction were present during the hospital admission.

Five days after sirolimus initiation, routine laboratory testing indicated subtherapeutic sirolimus concentrations (below limit of detection, 1 ng/mL) and improving kidney function. Serum creatinine decreased back to his prior baseline of 1.4 mg/dL. At his follow-up visit 6 days after sirolimus initiation, his weight had increased to 86.5 kg from a discharge weight of 81 kg, which was attributed to the high dose corticosteroids he received. No peripheral edema or abnormalities on pulmonary examination were noted at this time.

Nine days after sirolimus initiation, the patient was admitted for an elective rituximab infusion to address the non-human leukocyte antigen antibody-mediated component to his rejection. This infusion was cancelled because of new sore throat, cough, and chills. On examination, he was febrile, hypertensive, and tachycardic. His weight had increased to 90.5 kg for a total of 9.1 kg interval weight gain over a 9-day period. His serum creatinine was 1.54 mg/dL and serum albumin was 3.5 g/dL. Inflammatory markers included a C-reactive protein of 2.1 mg/dL and white blood cell count of $9.6 \times 10^3/\text{mcL}$, which remained stable during the hospital course. His urine dipstick was negative for protein. The patient was in mild respiratory distress with tachypnea and increased work of breathing and had mild bilateral lower extremity edema. Bilateral crackles were auscultated on pulmonary examination.

Within 12 hours of admission the patient developed moderate respiratory distress and hypoxemia. A comprehensive respiratory viral panel for immunocompro-

mised patients, rapid streptococcal test, and blood and urine cultures were all negative. Chest radiograph revealed bilateral patchy pulmonary opacities (Figure 1). Per recommendations of Infectious Disease, he was started on the following broad-spectrum antibiotics for presumed pneumonia: cefepime 1 g IV daily, azithromycin 875 mg IV daily, vancomycin 1 g (dosed by serum concentrations for goal level between 10 and 15 mg/mL), and fluconazole 400 mg IV daily for 5 to 7 days. Ganciclovir 100 mg IV daily was continued until discharge as treatment for CMV. For pulmonary edema he was started on furosemide, initially a 40-mg IV bolus followed by an 80-mg IV bolus and then by a 0.05 mg/kg/hr IV continuous infusion.

Over the next 6 hours, the patient's respiratory condition worsened, necessitating intubation. Hemodialysis was performed due to fluid overload, worsening kidney function, and radiological confirmation of pulmonary edema. Although the sirolimus trough concentration, drawn appropriately at 24 hours, was below goal level at 1.1 ng/mL, sirolimus was held due its known association with pneumonitis. Cardiac evaluation demonstrated mildly reduced left ventricular systolic function, which were similar to pretransplant findings. Bronchoscopy was performed and revealed a thick mucus plug and friable mucosa, but no overt signs of infection. Bronchoalveolar lavage revealed <72 copies/mL (limit of quantification) of human herpes virus-7 DNA. Serum CMV polymerase chain reaction was positive at 631 copies/mL but had decreased from the previous hospitalization.

After 3 sessions of hemodialysis for ultrafiltration, the pulmonary edema improved, and the patient was successfully extubated (Figure 2). All cultures were negative. The patient returned to his baseline status 10 days after his initial catastrophic event, and his renal function improved to baseline. He was discharged on a maintenance immunosuppressive regimen of long-acting tacrolimus and prednisone.

Figure 1. Radiological findings at baseline (left), during respiratory decompensation (middle), and after 3 rounds of hemodialysis (right).

Discussion

Following the algorithm of Naranjo et al,⁹ our patient had a probable adverse drug reaction in the form of an interstitial pneumonitis related to sirolimus. We came to this conclusion by assigning points for previous conclusive reports on the reaction, appearance of the adverse reaction after drug initiation, reaction improvement after drug discontinuation, lack of alternative causes and radiographically confirmed adverse event (Table S).

Furthermore, using previously published criteria, a definitive diagnosis of sirolimus-induced lung toxicity is highly likely.^{4,10} Only limited cases of sirolimus-induced lung toxicity have been reported in the pediatric age group (3—renal transplants, 1—liver transplant, 2—multivisceral transplants, 1—heart transplant).^{11,12}

Previously described cases of sirolimus-induced pneumonitis demonstrated a wide spectrum of clinical presentations including being noted incidentally to being associated with a range of symptoms such as

Figure 2. Timeline of events and trends in renal function and weight over the course of the hospitalization.

BUN, blood urea nitrogen; SRL, sirolimus

■ BUN; ▲ Weight; ● Creatinine

Table 2. Comparison Between Adult and Pediatric Sirolimus-Induced Pneumonitis Reported Risk Factors*

	Adult	Pediatric
Sirolimus dose	>5 mg/day	0.1 and 0.18 mg/kg/day
Sirolimus trough concentrations	>15 ng/mL	1.1–12.2 ng/mL
Sirolimus loading dose	Usually administered	Not reported
Recent increase of sirolimus dose/level	Yes	Not reported
Timing of sirolimus initiation posttransplant	Late sirolimus exposure	All reported episodes within 1 year of sirolimus initiation
Presence of allograft dysfunction	Yes	Not consistently reported
Volume overload	Yes	Not consistently reported
Sex	Male	Not consistently reported, at least 2 boys and 2 girls

* Modified with permission from Morath et al.¹⁵

cough, fever, and patchy opacities on chest radiography non-responsive to antibiotic therapy.^{13,14} This case shares similarities to previously described cases of sirolimus-induced lung toxicity in that our patient had allograft dysfunction, hypervolemia, and late exposure to sirolimus at the time of diagnosis.¹⁵ Differences from more frequently cited risk factors for sirolimus-induced pneumonitis include subtherapeutic sirolimus concentrations, short duration of therapy, and young patient age.¹⁶ However, sirolimus-induced pneumonitis with sirolimus concentrations within recommended range have been reported previously.¹⁷

Upon close review of published cases of sirolimus-associated pneumonitis, we found that even very low sirolimus concentrations at time of pneumonitis are not uncommon. Despite the fact that some reports do not mention the sirolimus value at time of diagnosis or only provide a range for their case series, we identified at least 12 patients with an sirolimus concentration <8 ng/mL at time of diagnosis.^{16,18–24} Conversely, we found only 12 patients with a confirmed sirolimus concentration >16 ng/mL.^{8,10,15,22,26–31} Thus, we did not find the predominance of high sirolimus concentrations that would be expected in a dose-dependent toxicity. Furthermore, we found 6 reported cases of patients developing sirolimus-induced pneumonitis within the first month of sirolimus initiation.^{7,21,27,28,32,33} These data suggest that initially reported risk factors might have been biased by small sample size. Especially when looking at pediatric case reports, the previously cited risk factors were not replicated (Table 2).¹⁶ In addition, although peripheral edema is known to be associated with sirolimus, significant pulmonary edema as noted in our patient is less often described.^{2,34} The patient had no proteinuria or significant hypoalbuminemia, which makes a diagnosis of secondary nephrotic syndrome due to sirolimus also less likely. It is unclear if our patient developed peripheral edema due to direct sirolimus effects, but with a C-reactive protein of 2.1 mg/dL and a white blood cell count of $9.6 \times 10^3/\text{mCL}$, systemic

inflammation and capillary leak seems unlikely.

Other mechanisms for sirolimus-associated interstitial pneumonitis that have been proposed include exposure to cryptic antigens, autoimmune response due to sirolimus blockade of epithelium repair, or a T-cell mediated, delayed-type hypersensitivity reaction.^{4,5,15,33} The extremely low sirolimus trough concentration and the patient's history of autoimmunity and hypersensitivity to multiple drugs seem to point toward such an immune-mediated mechanism, as opposed to dose-dependent toxicity. Of note, successful switch from sirolimus to everolimus has previously been reported. The lack of cross-reactivity was attributed to the less hydrophilic everolimus being less likely to cause hypersensitivity type reactions.^{35,36} Although inhibition of mechanistic target of rapamycin complex 1 with sirolimus has been shown to suppress the adaptive immune system by blocking the proliferation of T-effector cells, an exaggerated activation of the innate arm of the immune system has also been reported.^{37–39} Therefore, sirolimus-induced pneumonitis may be mediated through the innate arm as opposed to the adaptive arm of the immune system.

Interactions between corticosteroids and sirolimus in the innate arm of the immune system have been described.³⁹ Specifically, there is demonstrated antagonism with antigen processing between sirolimus and glucocorticoids at the cellular level in both monocytes and peripheral myeloid dendritic cells.⁴⁰ These observations raise the possibility of increased susceptibility to sirolimus toxicity in patients pretreated with glucocorticoids, especially at high doses. Given that our patient received high doses of corticosteroids for 2 weeks prior to his respiratory failure, this may have placed him at an increased risk.

Sirolimus and tacrolimus are known to interact with each other, and in the setting of high levels, could potentiate the adverse effect profile including precipitation of renal injury.^{41,42} Despite this, we have used combination sirolimus and lower dose tacrolimus-based

regimens to minimize nephrotoxicity posttransplant at our center. This experience has also been published by others.⁴² Future studies, perhaps originating from pediatric nephrology consortia to allow for increased numbers of patients, should explore whether risk factors for the development of sirolimus-induced pneumonitis differ in children from that of the adult transplant recipient population.

Conclusion

Sirolimus-induced pneumonitis is an important diagnosis to be considered in any transplant recipient receiving sirolimus with new onset fever, cough, or respiratory distress without an identifiable infectious source. The underlying mechanism remains unclear, complicating risk stratification. Further studies addressing the effect of glucocorticoids and sirolimus on the innate immune system and mechanisms of sirolimus toxicity are necessary.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. The case was approved by the Institutional Review Board at the University of Miami as part of the Predictors of Long-term Survival of Kidney Transplants in Children Project, which collects data on several outcome measures including adverse drug reactions.

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Supplemental Material

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