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CASE REPORT
Heart failure

Case Report: tacrolimus toxicity in the setting of concurrent Paxlovid use in a heart-transplant recipient

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Background Tacrolimus toxicity in patient's status post-orthotropic heart transplantation is not commonly reported. Given its narrow therapeutic window and drug–drug interactions, it must be closely monitored by providers who are experienced in transplant management. There are no case series of patients with tacrolimus toxicity in the setting of treatment for Sars-2-CoV-19 (COVID 19) for heart-transplant recipients. We present a case of tacrolimus toxicity in the setting of concurrent ritonavir–nirmatrelvir (Paxlovid) use.

Case summary The patient was a 74-year-old male with a prior significant history of heart transplantation and on maintenance immunosuppression with tacrolimus. He contracted COVID-19 and was prescribed antiviral therapy with Paxlovid by an outside provider prior to admission. The patient complained of severe headaches, dehydration, and tremors. After eliminating acute intracranial processes with imaging, laboratory investigation revealed a severely elevated tacrolimus level with acute renal injury. The patient was taken off tacrolimus and treated conservatively with intravenous hydration. The symptoms improved, particularly the headaches. He was discharged with instructions to resume his home dosing of tacrolimus and return to clinic in 1 week with a repeat trough level. The subsequent trough level was no longer supra-therapeutic.

Discussion Tacrolimus has a potent drug-drug interaction with Paxlovid (ritonavir-nirmatrelvir) and can be supra-therapeutic. Toxicity is associated with multiple adverse effects, including but not limited to, acute renal injury, neurotoxicity, and infections due to over-immunosuppression. As Paxlovid is effective in treating Sars-2-CoV-19 in heart-transplant recipients, knowledge and understanding of drug-drug interactions is crucial in preventing and mitigating toxicity.

Keywords Case Report • Tacrolimus • Paxlovid • CYP3A4 • Toxicity

ESC Curriculum 6.5 Cardiomyopathy • 8.5 Primary prevention

Learning Points

- Tacrolimus has a potent drug–drug interaction with Paxlovid (ritonavir–nirmatrelvir) and can be supra-therapeutic. Toxicity is associated with multiple adverse effects, including but not limited to, acute renal injury, neurotoxicity, and infections due to over-immunosuppression.
- With Sars-2-CoV-19 still in its pandemic phase, knowledge and understanding of drug–drug interactions between antiviral therapeutics and immunosuppressants are crucial in preventing and mitigating toxicity.

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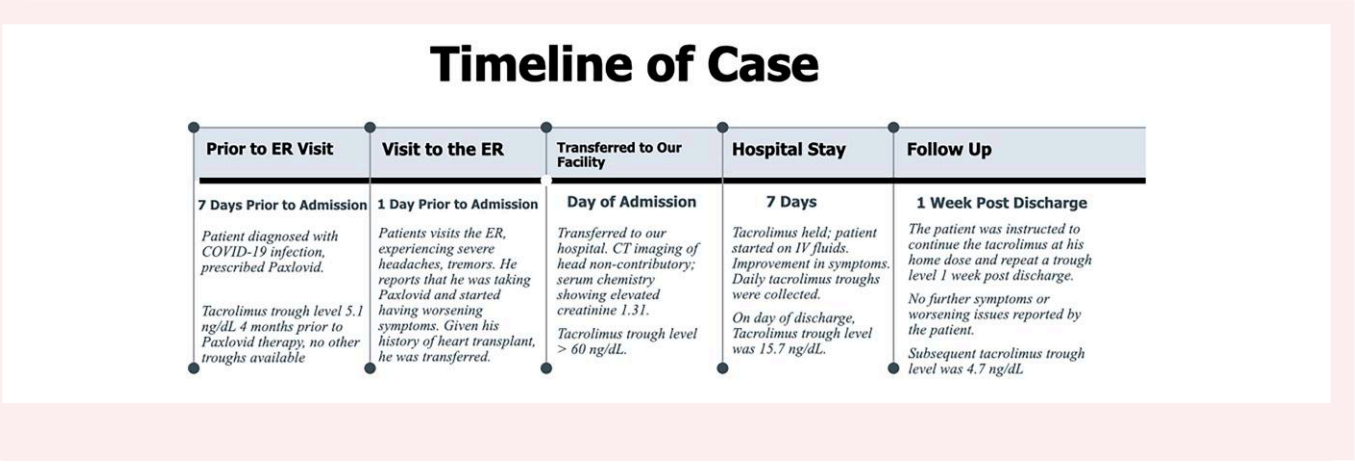
Introduction

Transplant patients are vulnerable to adverse events secondary to drug–drug interactions for several reasons. They take multiple medicines, including immunosuppressants with a narrow therapeutic window.[1] Tacrolimus has a narrow therapeutic index, and drug interactions are known to significantly impact pharmacokinetics.[2] We present a case of tacrolimus toxicity in a heart-transplant recipient, mediated by the use of nirmatrelvir/ritonavir (Paxlovid). The incidence is very rare given the newness of Paxlovid, which is currently authorized for emergency use by the Food and Drug Administration (FDA). The aim of the case is to illustrate the importance of assessing drug–drug interactions in transplant patients who are prescribed with antiviral and monoclonal antibody treatment for COVID-19 infection as well as lay out approaches to monitoring and treating immunosuppressant drug toxicity.

Timeline



Case report

The patient was a 74-year-old male who underwent heart transplantation in 2016 and presented to our facility as a direct transfer for headaches, acute renal injury, and tremors. Four months prior to admission, he had a routine echocardiogram and coronary angiogram for post-transplant surveillance, with no focal abnormalities reported. For transplant immunosuppression, he was taking tacrolimus 1 mg twice daily and mycophenolate mofetil 500 mg twice daily. The patient was not taking any antibiotic or antifungal medications.

He was diagnosed with COVID via rapid testing 7 days prior to admission and was prescribed Paxlovid nirmatrelvir 300–ritonavir 100 mg twice daily by an outside, non-transplant provider for a 5-day course. During that time, the patient noticed worsening headaches, vertigo-like symptoms, and a metallic taste in his mouth. The headaches did not relieve with acetaminophen therapy. During that time while he was taking Paxlovid, he continued to take his home dose of tacrolimus (1 mg twice daily). There was no collected serum creatinine, tacrolimus trough level, or random tacrolimus level at the time he was prescribed with Paxlovid. His last creatinine was one month prior to Paxlovid and was 1.2 mg/dL (normal $\leq$ 1.2 mg/dL) with a blood urea nitrogen of 19 mg/dL (normal $\leq$20 mg/dL). His last trough was 5.1 ng/mL (goal 4–6 ng/mL) four months prior to admission. The patient initially went to his local facility with these symptoms. Given his history of heart transplant and established relationship with our transplant program, he was transferred here for further management (*Figure 1*).

On examination, the patient was alert and oriented. He endorsed headaches but did not have limb weakness, numbness, tingling, or dysphagia. He did endorse mild tremors (hand tremors noted bilaterally) but denied chest pain, trouble breathing, or fluid retention. On admission, his vitals were recorded. He was afebrile with a temperature of 36.3°C, and the blood pressure was elevated with a reading of 149/86 mm Hg. He maintained a normal oxygen saturation of 96% on ambient air. The cardiovascular examination revealed a regular rate and rhythm without any concerning murmurs, rubs, or gallops. At that point, the differential for his constellation of symptoms included dehydration, atypical migraine, and accelerated hypertension with symptoms.

Serum chemistry, complete blood count, and a tacrolimus morning trough level were obtained. His serum chemistry noted a mildly elevated creatinine level of 1.31 mg/dL with a blood urea nitrogen of 31 mg/dL. Complete blood count was unremarkable. His serum tacrolimus level was recorded as >60 ng/mL (an exact measurement could not be obtained as the value exceeded this laboratory limit). A non-contrasted computerized tomography scan was obtained of the head, which revealed no acute intracranial abnormalities.

The tacrolimus was held during his hospitalization. He was started on intravenous hydration with lactated ringers at 100 mL/h for 10 h initially on Day 0 of the hospital stay. He received intravenous 0.9% normal saline at 100 mL/h for 10 h daily for three additional doses. No additional therapies were used to address the supra-therapeutic tacrolimus level. There were no specific therapies required for management of patient's COVID-19. His oxygen saturation was normal, and he was not in respiratory distress. The patient's headache improved. Standard strength acetaminophen was used on a parenteral basis to treat the headache. Daily labs showed a decline in his trough levels. The hand tremor persisted but was mild in severity. Both the serum creatinine and blood urea nitrogen levels also normalized. The patient still had an elevated level of tacrolimus, 15 ng/dL, on the day of discharge, but he was asymptomatic and instructed to resume the tacrolimus at his home dosing. He was scheduled to return to the clinic in 1 week and repeat a trough level. The patient did return to clinic 1 week after discharge, and his trough level, obtained 10 days post-discharge, was 4.7. He did not report any further adverse events and that the headaches and tremors had resolved.

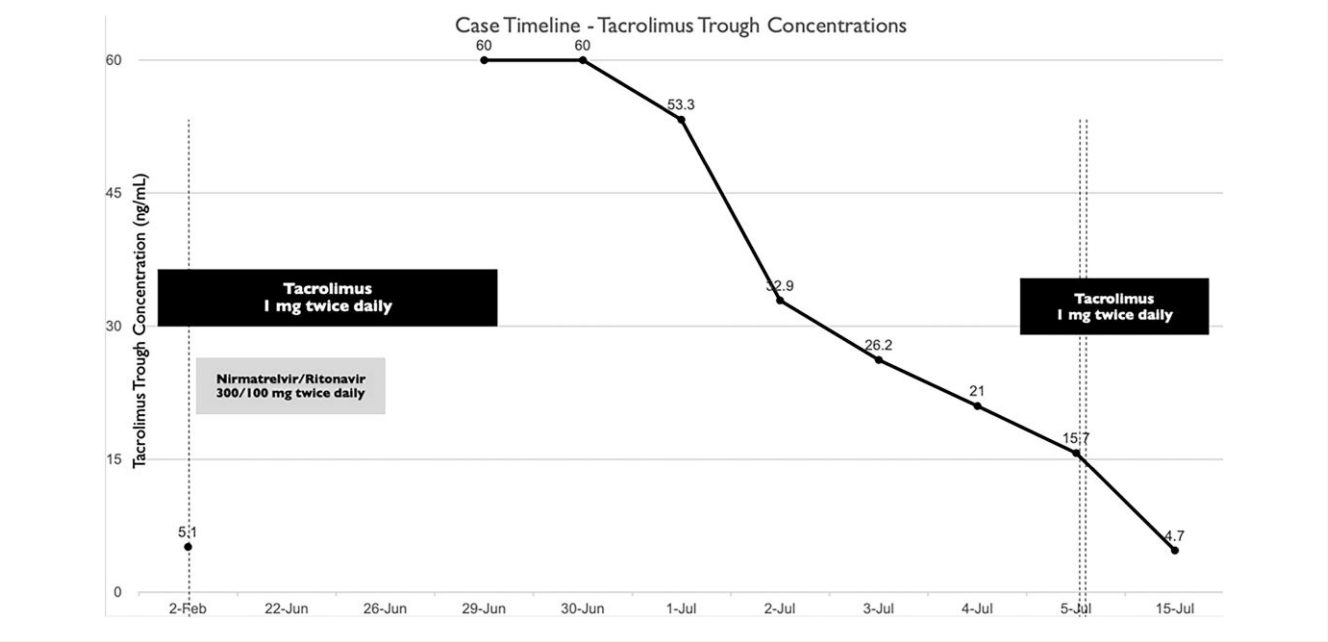


Figure 1 Graph of tacrolimus trough levels. The line graph showed the initial tacrolimus trough level prior to Paxlovid therapy followed by subsequent trough levels after completing therapy while on tacrolimus. The final value illustrates the resolution in toxicity after holding tacrolimus. The July 5th value was the final trough level on the day of discharge. The patient's last tacrolimus level at our facility was 4 months prior to his admission and was normal. Paxlovid was used from 6/22 to 6/27. This is the revised document with marked changes noted in either bold or underlined (as in the *Legends* section). In addition, the citations used were included in superscript within the body of the *Discussion* section.

Discussion

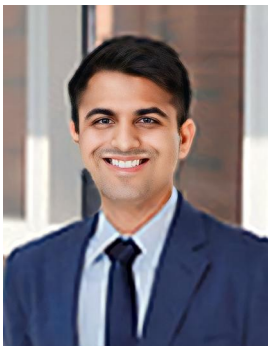
There have been two reported cases of tacrolimus toxicity in patients taking Paxlovid.[3] In both cases, the patients did not undergo orthotropic heart transplant. In the first case, the patient's tacrolimus dosing was pre-emptively reduced while the second patient did not receive the full Paxlovid course before encountering symptoms.[3] Our patient did complete a full course of Paxlovid and developed symptoms during and after therapy. He continued taking tacrolimus up to the day of admission. All three patients had tacrolimus concentrations >60 ng/dL. To our knowledge, this is the first reported case involving a heart-transplant recipient.

Tacrolimus is metabolized by the CYP3A4 enzyme pathway, and levels are reduced with CYP3A4 inducers and elevated with CYP3A4 inhibitors.[4] Paxlovid contains ritonavir, which is a potent CYP3A4 inhibitor. Paxlovid is produced by Pfizer Labs, and the fact sheet on Paxlovid does note that concomitant use of tacrolimus with Paxlovid does lead to elevated levels of the former.[5] While there are comments related to dosing Paxlovid based on the patient's creatinine clearance with an advisory on not administering it with a creatinine clearance <30,[6] there are no set guidelines for how long to hold tacrolimus or reduce dosing. Discontinuation of Paxlovid reduces CYP3A4 inhibition by up to 60% in the first 24 h and up to 90% by Day 5.[6] Upon learning that the patient had a markedly supra-therapeutic level of tacrolimus, his tacrolimus was held. He had already completed his course of Paxlovid prior to the transfer. However, complete resolution of CYP3A4 enzyme activity may not occur until three weeks.[7] A recent Letter to the Editor in the American Journal of Transplantation laid out an approach of holding tacrolimus for 5 days while administering Paxlovid.[8] The Paxlovid product label advises against co-administration with tacrolimus but does not provide further guidance as far as duration of holding or modification to tacrolimus dosing.[5] Given the difficulty in outpatient daily monitoring of tacrolimus, particularly when the affected patient would need to quarantine due to COVID-19, a black box warning that this medicine is contraindicated with tacrolimus can help prevent more cases of tacrolimus toxicity.

Earlier cases noted the use of rifampin in treating the toxicity as it is a potent CYP3A4 inducer and can serve as an antidote.[9] Alternatively, phenytoin has also been proposed as an antidote for treating tacrolimus toxicity given its likewise potent CYP3A4 induction, documented in a case series including four patients treated with phenytoin without phenytoin-related effects.[10] Given that our patient responded nicely to conservative management by holding the drug along with IV fluids, we elected not to pursue this route of treatment.

This case highlights the possible danger of outpatient Paxlovid prescriptions by providers unfamiliar with immunosuppression medications. Risk mitigation strategies are important in minimizing drug–drug interaction. These include educational outreach to providers who may care for transplant patients, informing local pharmacies to cross check Paxlovid with the patient's current regimen, and automated reporting to prescribers of tacrolimus and other calcineurin inhibitors when their practice patients are prescribed Paxlovid.[3] As the SARS-CoV-2 (COVID 19) continues to cause significant mortality and morbidity, including patients status post-solid organ transplantation and on immunosuppression, awareness of potential drug–drug interactions with therapeutics approved to treat COVID 19 is important amongst all providers. Ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19.[11] Use of nirmatrelvir/ritonavir in patients treated with tacrolimus can be considered, so long as there is a proactive plan in place to minimize toxicity risk by empirically modifying the tacrolimus dosing during use.

Lead Author biography



I am Sujal Modi, a fellow in Advanced Heart Failure and Transplant at The Ohio State University Wexner Medical Center, Columbus, OH. I have completed my medical school, internal medicine, and general cardiology fellowship training at West Virginia University, Morgantown, WV. I have given oral/poster presentations in various conferences, including the national ACC meeting. My clinical and research interests include interventional heart failure, cardiogenic shock, mechanical circulatory support, and teaching. In my spare time, I enjoy time with family and friends, caring for my dog, reading, exercising, and spending time outdoors.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

References

1. Gago-Sánchez AI, Font P, Cárdenas M, Aumente MD, Del Prado JR, Calleja MÁ. Real clinical impact of drug–drug interactions of immunosuppressants in transplant patients. *Pharmacol Res Perspect* 2021;**9**:e00892.
2. Christians U, Jacobsen W, Benet L, Lampen A. Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet* 2002;**41**:813–851.
3. Fishbane S, Hirsch JS, Nair V. Special considerations for Paxlovid treatment among transplant recipients with SARS-CoV-2 infection. *Am J Kidney Dis* 2022;**79**:480–482.
4. Katzenmaier S, Markert C, Riedel K-D, Burhenne J, Haefeli WE, Mikus G. Determining the time course of CYP3A inhibition by potent reversible and irreversible CYP3A inhibitors using A limited sampling strategy. *Clin Pharmacol Ther* 2011;**90**:666–673.
5. *Fact sheet for healthcare providers: emergency use authorization for Paxlovid TM 5*. New 6 York, NY: Pfizer, Inc.; 2021.
6. Lange NW, Salerno DM, Jennings DL, Choe J, Hedvat J, Kovac DB, *et al.* Nirmatrelvir/ritonavir use: managing clinically significant drug–drug interactions with transplant immunosuppressants. *Am J Transplant* 2022;**22**:1925–1926.
7. Stader F, Khoo S, Stoeckle M, Back D, Hirsch H, Battegay M, *et al.* Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. *J Antimicrob Chemother* 2020;**75**:3084–3086.
8. Salerno DM, Jennings DL, Lange NW, Kovac D, Shertel T, Chen JK, *et al.* Early clinical experience with nirmatrelvir/ritonavir for the treatment of COVID-19 in solid organ transplant recipients. *Am J Transplant* 2022;**22**:2093–2099.
9. Rose D, Gandhi S, Bedard R, Mondy K, Chu A, Gamble K, *et al.* Supratherapeutic tacrolimus concentrations with nirmatrelvir/ritonavir in solid organ transplant recipients requiring hospitalization: a case series using rifampin for reversal. *Open Forum Infect Dis* 2022;**9**:ofac238.
10. Jantz AS, Patel SJ, Suki WN, Knight RJ, Bhimaraj A, Gaber AO. Treatment of acute tacrolimus toxicity with phenytoin in solid organ transplant recipients. *Case Rep Transplant* 2013;**2013**:375263.
11. Bhimraj A, Morgan R, Shumaker AH, Lavergne V, Baden L, Cheng VCC, *et al.* Infectious Disease Society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis* 2020;**478**:1–13.