BMC Pediatrics

CASE REPORT Open Access

Tacrolimus-induced interstitial lung injury in a pediatric cardiac transplant recipient: a case report and literature review

Qian-Nan Zhang[1], Xiang-Hong Zhang[1] and Shan-Shan Shi[1*]

Abstract

Background Tacrolimus-induced interstitial lung injury (TI-ILI) is a rare but potentially fatal adverse effect of calcineurin-inhibitor therapy. To our knowledge, TI-ILI has not previously been reported in a paediatric heart-transplant recipient.

Case presentation A 6-year-old boy with PLN-related dilated cardiomyopathy underwent orthotopic heart transplantation. Maintenance immunosuppression comprised tacrolimus, mycophenolate mofetil and prednisone. On post-operative day 13 he developed bilateral ground-glass opacities with interlobular septal thickening on chest CT. Broncho-alveolar lavage metagenomics showed only low-abundance Pseudomonas aeruginosa and Acinetobacter baumannii; extensive microbiological, cardiac work-up was negative. Infiltrates progressed despite targeted antibiotics, but resolved within 4 weeks after tacrolimus was replaced by cyclosporine and corticosteroids were doubled. No relapse occurred during 6 months of follow-up.

Conclusions TI-ILI should be considered in any heart transplant recipient with unexplained progressive bilateral pulmonary infiltrates. Early tacrolimus withdrawal and prompt corticosteroid therapy are associated with complete recovery; re-exposure to tacrolimus is contraindicated.

Keywords Tacrolimus, Pulmonary injury, Cardiac transplantation, Pediatric patients

Introduction

Tacrolimus is a first-line immunosuppressive agent frequently used to prevent rejection after paediatric heart transplantation. It binds the intracellular receptor FKBP12; the resulting complex selectively inhibits calcineurin phosphatase, thereby disrupting calcium-dependent signalling in T-lymphocytes and suppressing transcription of key cytokines such as interleukin-2 and −6 [1, 2]. Although the efficacy of tacrolimus in averting acute cellular rejection is well established [3], its use is accompanied by a recognised spectrum of adverse effects that includes nephrotoxicity, neurotoxicity, gastrointestinal disturbance, haematological abnormalities, hypertension and post-transplant lymphoproliferative disorder. By contrast, tacrolimus-related pulmonary toxicity is rarely reported, and to our knowledge, has not been described in children after cardiac transplantation. We present a 6-year-old heart-transplant recipient who developed tacrolimus-induced interstitial lung injury fulfilling the 2018 Fleischner Society criteria for drug-induced interstitial lung disease [4].

*Correspondence:
Shan-Shan Shi
sicu1@zju.edu.cn
[1]Department of CICU, National Clinical Research Center for Children and Adolescents' Health and Diseases, Children's Hospital, Zhejiang University School of Medicine, No. 3333, Binsheng Road, Hangzhou 310052, China

Case presentation

The patient was a 6-year 9-month-old Chinese boy (weight 26.0 kg) with glucose-6-phosphate dehydrogenase deficiency. At age 4 he was admitted for congestive heart failure and diagnosed with dilated cardiomyopathy after complete evaluation. Whole-exome sequencing revealed a pathogenic PLN mutation (c.43G > A). While waiting for transplantation he developed recurrent ventricular arrhythmia and asystole secondary to refractory heart failure, requiring cardiopulmonary resuscitation.

On arrival he was sedated, afebrile (36.1°C), blood pressure 125/68 mmHg, heart rate 110 beats min^{-1}, respiratory rate 26 breaths min^{-1}. Bibasal fine crackles were heard; heart sounds were muffled without murmurs. There was no peripheral oedema. Echocardiography showed severe left-ventricular dilatation (ejection fraction 18.9%) and systolic dyssynchrony. He was immediately intubated and placed on veno-arterial ECMO.

Forty-five days later, the patient underwent orthotopic heart transplantation with delayed sternal closure. Induction immunosuppression consisted of basiliximab (10 mg) and intravenous methylprednisolone. A standard triple-drug maintenance regimen comprising tacrolimus, mycophenolate mofetil, and prednisolone was initiated 48 h post-operatively. The initial tacrolimus dose was 0.07 mg kg^{-1} day^{-1}, subsequently adjusted to maintain trough concentrations of 5–16.1 μg L^{-1} (Fig. 1). Veno-arterial ECMO was weaned and discontinued on post-operative day (POD) 4; the patient was successfully extubated on POD 9 and transitioned to non-invasive ventilatory support.

On POD 13, the patient developed rapid atrial tachycardia requiring re-intubation. Chest CT (Fig. 2C, D) revealed diffuse bilateral ground-glass opacities with interstitial thickening. Serum galactomannan and β-D-glucan assays were negative, and metagenomic next-generation sequencing of bronchoalveolar lavage fluid detected only low-abundance commensal organisms, with no evidence of viral, fungal, or parasitic pathogens. Despite broad-spectrum antimicrobial therapy, pulmonary infiltrates persisted even as inflammatory markers declined (Fig. 3). Tracheostomy was performed on POD 24.

To contextualize the post-operative pulmonary findings, review of the preoperative imaging and procedural records was undertaken. Preoperative chest CT (Fig. 2A,

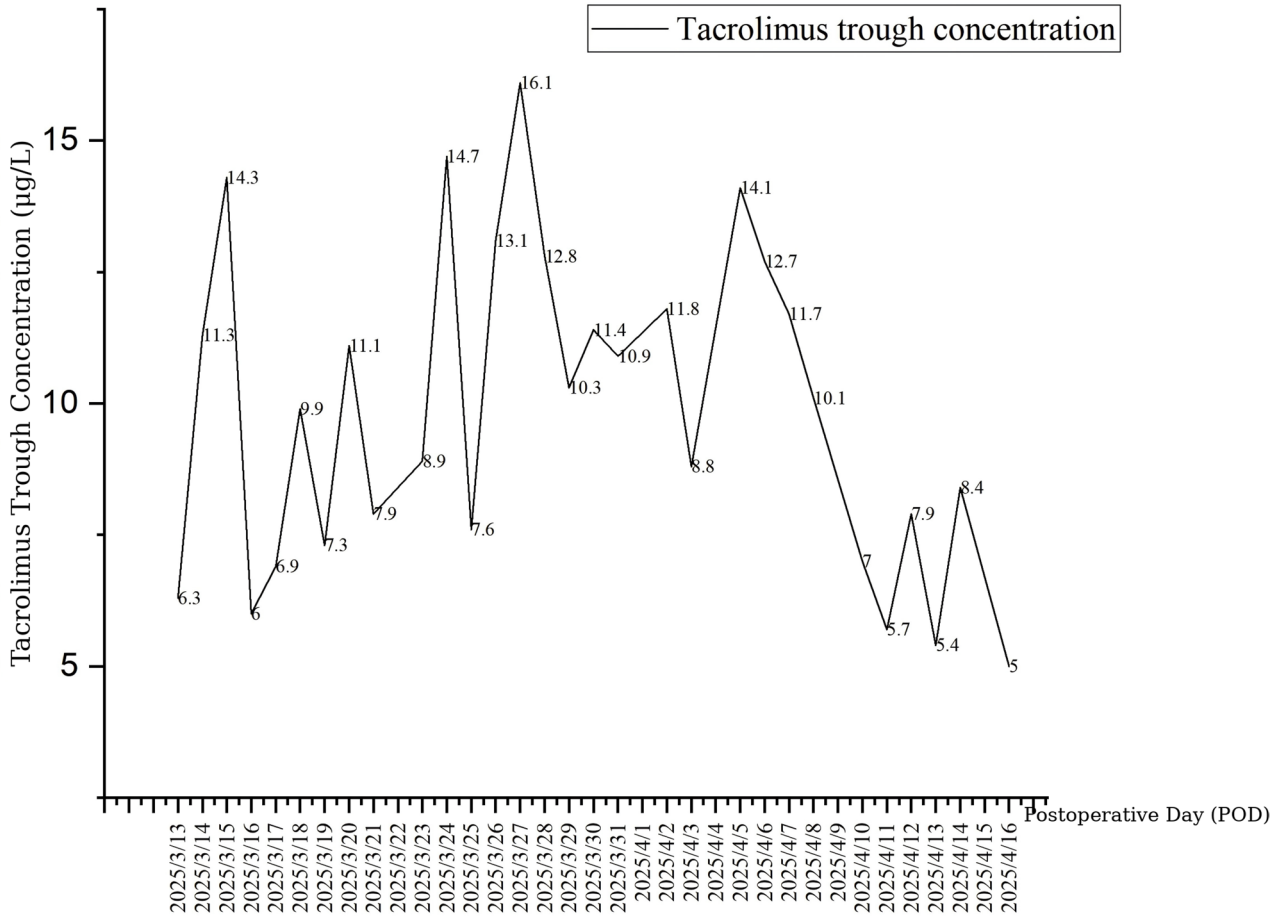

Fig. 1 Tacrolimus trough concentration monitoring from postoperative day (POD)5 (March 13, 2025) to POD 38. Abbreviations: POD, postoperative day

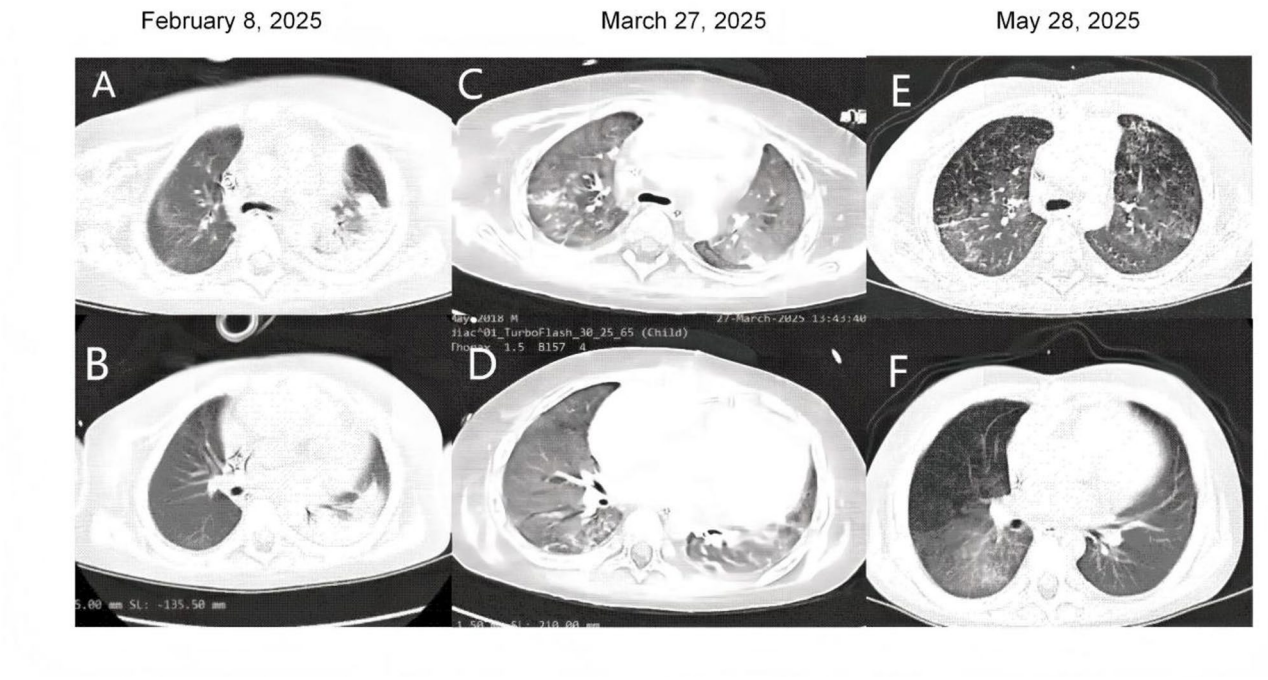

Fig. 2 A relatively normal thoracic computed tomography (CT) scan at the initiation of tacrolimus treatment in February 2025 **A**, **B**. In March 2025, during TI-ILI, the CT revealed multiple infiltrations, extensive pulmonary ground-glass opacities, and interstitial lung disease **C**, **D**. Discontinuation of Tacrolimus and oral prednisolone resulted in complete recovery, as evidenced by the resolution of infiltrations on chest CT prior to discharge in May 2025 **E**, **F**. Abbreviations: CT, computed tomography; TI-ILI, tacrolimus-induced interstitial lung injury

B) had demonstrated segmental consolidation with atelectasis in the left lower lobe. Concurrent bronchoscopy revealed narrowing and flattening of the left main bronchus, which was attributed to extrinsic compression from left cardiac enlargement. Following two preoperative bronchoscopic bronchoalveolar lavage procedures, cardiac transplantation effectively relieved this extrinsic compression; postoperative chest CT confirmed marked resolution of the left lower lobe consolidation and atelectasis. Serial bronchoscopic examinations on POD 53 and POD 63 demonstrated patent airways without stenosis or appreciable increase in secretions. In contrast, the newly emerging bilateral interstitial changes on postoperative chest CT (Fig. 2C, D), interpreted alongside tacrolimus exposure, the patient's clinical trajectory, and the absence of identifiable infectious aetiology, were attributed to drug-induced pulmonary toxicity.

Given that infection had been exhaustively excluded and the temporal relationship strongly implicated drug toxicity, tacrolimus was discontinued on POD 40 and replaced with cyclosporine; the prednisolone dose was simultaneously doubled. Follow-up chest CT (Fig. 2E, F) demonstrated progressive resolution of the pulmonary infiltrates. The tracheostomy was decannulated one month later, with full recovery of respiratory function. Corticosteroids were gradually tapered, and the patient was discharged in stable condition.

Discussion

We describe the first paediatric case of tacrolimus-induced interstitial lung injury after heart transplantation, diagnosed by rigorous exclusion and successfully managed by early drug withdrawal and corticosteroid therapy.

Common causes of new pulmonary infiltrates after paediatric heart transplantation are infection, cardiogenic oedema and drug-induced interstitial lung disease (DI-ILD). Our patient had prolonged ICU exposure and intensive immunosuppression, so infection was the leading hypothesis. Yet metagenomic sequencing of bronchoalveolar lavage showed only scant commensal bacteria, and the infiltrates progressed despite broad-spectrum antimicrobial therapy. Haemodynamics remained stable despite aggressive diuresis, and echocardiography demonstrated normal graft function, arguing strongly against cardiogenic pulmonary oedema. An even more intriguing feature was the striking dissociation between radiological severity and clinical stability: despite near-whiteout opacities on CT, the patient maintained excellent oxygenation with PaO_2/FiO_2 ratios persistently > 400 mmHg. Consequently, DI-ILD became the most plausible explanation, especially when the lung lesions resolved promptly after tacrolimus withdrawal and corticosteroid intensification.

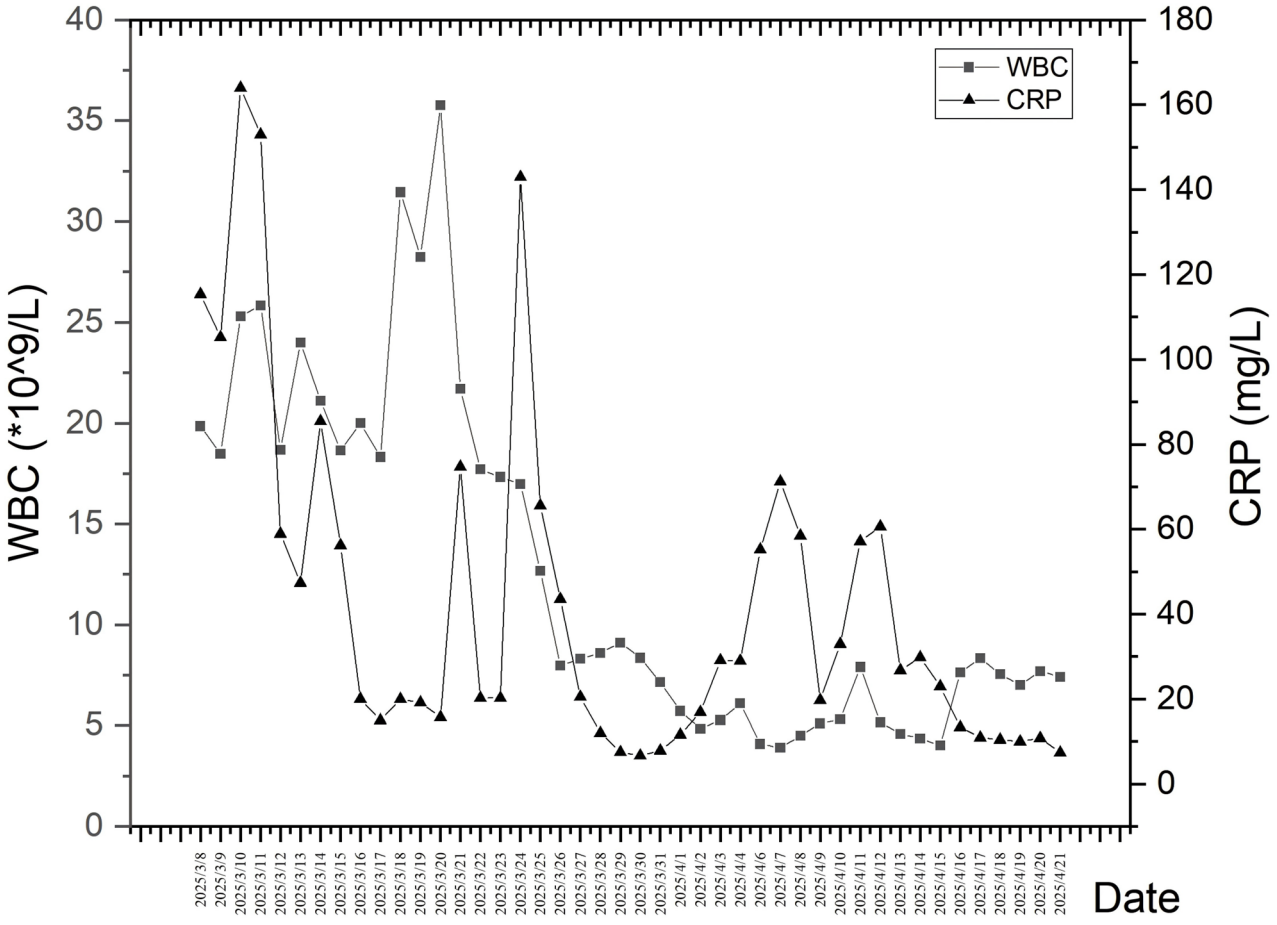

Fig. 3 Longitudinal trends in white blood cell count and C-reactive protein levels from postoperative day (POD) 0 (March 8, 2025) through POD 43. Abbreviations: WBC, white blood cell; CRP, C-reactive protein; POD, postoperative day

DI-ILD is a diagnosis of exclusion. The 2018 Fleischner Society criteria [4] require: (i) newly acquired bilateral pulmonary opacities on CT; (ii) temporal association with the implicated drug; and (iii) exclusion of competing aetiologies. Although no lung biopsy was obtained, the imaging pattern (bilateral ground-glass opacities with reticulation) and the brisk clinical response are consistent with non-specific interstitial pneumonia (NSIP), the commonest histological phenotype reported with tacrolimus. Proposed mechanisms include direct alveolar epithelial toxicity, immune dysregulation, cytokine release and oxidative stress [5].

Immediate cessation of the culprit drug is the cornerstone of therapy; corticosteroids are added when withdrawal alone fails to induce rapid improvement. Early recognition usually leads to complete recovery, whereas delayed diagnosis can precipitate irreversible fibrosis or fulminant acute respiratory distress syndrome.

Tacrolimus-induced interstitial lung injury (TI-ILI) is rare in children. Most published cases involve adult rheumatoid-arthritis patients with pre-existing interstitial lung disease and tacrolimus trough levels above or at the upper limit of the therapeutic range [6–8]. By contrast, our patient had no prior pulmonary pathology, and the majority of his tacrolimus concentrations were within the conventional target range (5–16 μg L^{-1}); a single transient peak (16.1 μg L^{-1}) coincided with the first radiological deterioration, suggesting that even brief supra-therapeutic exposure may trigger injury in susceptible individuals.

Only one paediatric case has been reported previously [9] : a 7-year-old who developed fatal obstructive bronchiolitis after heart transplantation; his tacrolimus level was markedly elevated (84 ng·dL^{-1}). Importantly, re-exposure to tacrolimus has been followed by more severe, occasionally fatal, recurrences. Among ten adult TI-ILI cases described by Japanese investigators, three patients were inadvertently rechallenged; all experienced a second, more aggressive pulmonary event, and the three deaths occurred in patients > 70 years whose imaging showed diffuse alveolar damage [7]. These observations underscore the need to avoid rechallenge and to substitute an alternative calcineurin inhibitor (e.g. cyclosporine) once TI-ILI is confirmed. Current evidence linking tacrolimus-associated interstitial lung injury (TI-ILI)

to pharmacokinetic exposure in heart-transplant recipients remains scarce and partly contradictory [10]: pulmonary toxicity has been described at trough concentrations as low as 5 $ng \cdot mL^{-1}$. Although routine therapeutic-drug monitoring (TDM) is standard practice because of the drug's narrow index, clinicians should maintain a high index of suspicion for TI-ILI even when levels lie within the conventional target range. Once TI-ILI is confirmed, re-exposure to tacrolimus is absolutely contraindicated.

A definitive lung biopsy was not performed in this patient, owing to rapid clinical deterioration and the prohibitive procedural risk associated with a post-cardiac-transplant child receiving multi-drug immunosuppression. The absence of histopathological confirmation means that the hypothesized non-specific interstitial pneumonia (NSIP) pattern, though supported by CT imaging characteristics and the overall clinical course, cannot be definitively established, representing an inherent limitation that introduces a degree of diagnostic uncertainty.

We further acknowledge that the pathogenesis of ILD in this patient was likely multifactorial. Pre-existing cardiogenic pulmonary congestion, surgical trauma, ischemia-reperfusion injury, and the broader immunosuppressive regimen may all have contributed to pulmonary injury to varying degrees. Nevertheless, the clear temporal relationship between tacrolimus initiation and ILI onset, the persistently supratherapeutic tacrolimus trough levels, and the marked clinical and radiological improvement following tacrolimus dose reduction, which achieved without modification of any other immunosuppressants, collectively and strongly implicate tacrolimus as the predominant causative agent in this case.

It should also be noted that, although cardiac transplantation theoretically afforded a concurrent opportunity for intraoperative lung biopsy, this approach was deemed inadvisable given the anticipated prolonged cardiopulmonary bypass time, the overriding need to prioritize hemodynamic stabilization, and the substantial risk of additional surgical complications in an immunocompromised pediatric patient. Intraoperative lung biopsy in this context carries well-recognized risks, including air leak, hemorrhage, and delayed wound healing, which were considered unacceptable in this clinical setting.

Future multicenter efforts to prospectively collect biopsy-proven pediatric TI-ILI cases would substantially advance understanding of the histopathological spectrum of this condition. The establishment of a dedicated registry for drug-induced ILD in pediatric solid organ transplant recipients is strongly warranted and encouraged.

Conclusion

Tacrolimus can cause life-threatening interstitial lung injury even in children with therapeutic drug levels and no pre-existing pulmonary disease. Unexplained bilateral ground-glass opacities after paediatric heart transplantation should prompt immediate tacrolimus withdrawal and high-dose corticosteroids. Re-exposure is absolutely contraindicated. We recommend routine trough-level monitoring be supplemented by systematic chest imaging during the first 6–8 post-transplant weeks to permit early recognition and reversible intervention.

Abbreviations

TI-ILI	Tacrolimus-induced interstitial lung injury
CT	Computed tomography
DCM	Dilated cardiomyopathy
ECMO	Extracorporeal membrane oxygenation
POD	Post-operative day
DI-ILD	Drug-induced interstitial lung disease
ICU	Intensive care unit
NSIP	Non-specific interstitial pneumonia
TDM	Therapeutic-drug monitoring

Acknowledgements

The authors thank the family for participating and supporting this study.

Authors' contributions

QNZ contributed to the original draft writing, visualization, and the review and editing of the manuscript. XHZ participated in the review and editing process. SSS was responsible for conceptualization, supervision, and also contributed to review and editing. All authors have approved the final version of the manuscript.

Funding

The authors did not receive any specific funding for this study.

Data availability

The data supporting the findings of this study can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was in compliance with the Helsinki Declaration and was approved by the Ethical Review Board of Children's Hospital, Zhejiang University School of Medicine

Consent for publication

The parents of the patient consented to the publication of the case and any accompanying images with written consent. Written informed consent was obtained from the parents of the patients for the publication of this study.

Competing interests

The authors declare no competing interests.

Received: 9 February 2026 / Accepted: 11 March 2026
Published online: 24 March 2026

References

1. Hussain Y, Khan H. Immunosuppressive drugs. In: Encyclopedia of infection and immunity. Elsevier; 2022. p. 726–40.
2. Gratreak BDK, Swanson EA, Lazelle RA, et al. Tacrolimus-induced hypomagnesemia and hypercalciuria requires FKBP12 suggesting a role for calcineurin. Physiol Rep. 2020;8(1):e14316.

3. Chand DH, Southerland SM, Cunningham RJ 3. Tacrolimus: the good, the bad, and the ugly. Pediatr Transpl. 2001;5(1):32–6.
4. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138–53.
5. Spagnolo P, Bonniaud P, Rossi G, Sverzellati N, Cottin V. Drug-induced interstitial lung disease. Eur Respir J. 2022;60(4):2102776. Published 2022 Oct 27.
6. Sasaki T, Nakamura W, Inokuma S, Matsubara E. Characteristic features of tacrolimus-induced lung disease in rheumatoid arthritis patients. Clin Rheumatol. 2016;35(2):541–5.
7. Koike R, Tanaka M, Komano Y, et al. Tacrolimus-induced pulmonary injury in rheumatoid arthritis patients. Pulm Pharmacol Ther. 2011;24(4):401–6.
8. Miwa Y, Isozaki T, Wakabayashi K, et al. Tacrolimus-induced lung injury in a rheumatoid arthritis patient with interstitial pneumonitis. Mod Rheumatol. 2008;18(2):208–11.
9. Karim F, Misra A, Sehgal S. Bronchiolitis obliterans organising pneumonia secondary to tacrolimus toxicity in a pediatric cardiac transplant recipient. Cardiol Young. 2023;33(4):630–2.
10. Braithwaite HE, Darley DR, Brett J, Day RO, Carland JE. Identifying the association between tacrolimus exposure and toxicity in heart and lung transplant recipients: A systematic review. Transpl Rev (Orlando). 2021;35(2):100610.

Publisher's Note