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REVIEW ARTICLES

Drug-Induced Leukopenia after Kidney Transplantation: Insights from Literature and a Clinical Case

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Abstract

Introduction: Leukopenia, particularly neutropenia, is a frequent hematological complication in kidney transplant recipients. It is most often related to immunosuppressive and prophylactic agents. These drugs are essential for preventing graft rejection and infection. However, they may induce myelosuppression. This leads to increased infection risk and often requires therapy modification.

Materials and Methods: We conducted a narrative review of the literature by searching PubMed, Embase, and Scopus for studies published between January 2010 and June 2024. Search terms included "leukopenia," "neutropenia," "drug-induced," "kidney transplantation," "mycophenolate," "valganciclovir," "tacrolimus," "cotrimoxazole," and "myelosuppression." Eligible studies involved adult kidney transplant recipients and reported drug-induced leukopenia.

Results: Eight key studies were identified. Mycophenolate mofetil, valganciclovir, and trimethoprim-sulfamethoxazole were the most frequent causative agents. Tacrolimus was occasionally implicated. Reported incidence of leukopenia ranged from 19% to 83% during the first post-transplant year. Neutropenia occurred in up to 48% of patients. Risk factors included CMV D+/R− serostatus, combination therapy, and higher drug dosages. To illustrate clinical complexity, we present a case of a 36-year-old renal transplant recipient. He developed severe leukopenia and neutropenia two months post-transplant. White blood cell counts normalized following therapy adjustment and G-CSF administration, without subsequent rejection or infection.

Conclusion: Drug-induced leukopenia is a common complication after kidney transplantation. It is seen particularly with mycophenolate and valganciclovir, and less often with tacrolimus. Early detection, individualized dose adjustment, and supportive therapies are essential. These measures balance infection prevention with adequate immunosuppression. Standardized management guidelines are lacking, highlighting the need for prospective studies.

Keywords: Kidney transplantation; Immunosuppressive, Tacrolimus; Mycophenolate mofetil; Valganciclovir

Introduction

Leukopenia, particularly neutropenia, is a significant hematological complication in kidney transplant (KT) recipients. The predominant etiology of leukopenia in this population stems from the use of immunosuppressive and prophylactic pharmacological agents. While these medications are indispensable for preventing allograft rejection and opportunistic infections, they are frequently associated with significant myelosuppression [1].

Common agents implicated in post-transplant leukopenia include mycophenolate mofetil (MMF), valganciclovir, trimethoprim-sulfamethoxazole (TMP-SMX), and, less commonly, tacrolimus [2, 3]. The development of leukopenia poses a dual threat: it increases

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susceptibility to severe infections and necessitates immunosuppressive dose adjustments, which may, in turn, elevate the risk of graft dysfunction or acute rejection [4].

The objective of this review is to provide an updated synthesis of current evidence regarding drug-induced leukopenia in adult kidney transplant recipients. We aim to clarify pathophysiological mechanisms, identify key risk factors, assess clinical implications, and explore effective strategies for prevention and management. These efforts are intended to optimize long-term transplant outcomes.

Literature Review

Drug-induced leukopenia (DIL)remains a common yet underrecognized complication in (KT recipients. Its incidence varies widely depending on the immunosuppressive and prophylactic regimen, therapy duration, and patient-specific risk factors. The condition often presents a diagnostic and therapeutic challenge, requiring a nuanced balance between maintaining immunosuppressive efficacy and avoiding hematologic toxicity.

Several key agents have been consistently implicated in DIL, including mycophenolate mofetil (MMF), valganciclovir, trimethoprim-sulfamethoxazole (TMP-SMX), and antithymocyte globulin (ATG), with tacrolimus playing a lesser but relevant role in some cases [5]. *Khalil et al. (2018)* provided a comprehensive overview of drug-induced cytopenias, emphasizing the importance of sequential drug withdrawal, close hematologic monitoring, and individualized immunosuppressive protocols to mitigate complications such as infections or graft loss [5].

Rios and Mead [6] presented a notable case in which tacrolimus was the likely cause of persistent leukopenia after exclusion of other agents, with full hematologic recovery upon switching to cyclosporine. This highlights tacrolimus's potential myelosuppressive properties, possibly mediated by pharmacokinetic or immunologic mechanisms.

In a systematic review of over 80 studies*, Raval et al*. [7] found neutropenia rates ranging from 13% to 48% and leukopenia (WBC < 3,500/μL) rates ranging from 19% to 83% during the first post-transplant year. Key risk factors included donor-positive/recipient-negative (D+/R−) CMV status, MMF, and tacrolimus. Leukopenia and neutropenia were strongly associated with increased rates of opportunistic infections, higher rates of acute rejection, and more frequent therapy adjustments. The use of granulocyte colony-stimulating factor (G-CSF) was commonly employed in severe cases, reflecting the clinical burden of hematologic toxicity.

Tacrolimus's indirect role in neutropenia was explored by *De Rycke et al*. [8], who proposed synergistic toxicity with MMF and modulation of cytokine signaling as possible mechanisms. They advocated for stepwise adjustments, beginning with MMF or valganciclovir dose reductions, before modifying tacrolimus therapy.

Bildac et al. [9] further reported a case of reversible neutropenia associated with tacrolimus, with resolution only after a switch to cyclosporine. These findings support a tailored approach to persistent cytopenias, particularly when conventional myelotoxic agents have already been discontinued.

Additional evidence from observational studies and meta-analyses supports an association between valganciclovir prophylaxis, MMF, and tacrolimus-based regimens and leukopenia. A 2024 meta-analysis [10] reported a pooled leukopenia incidence of 18% (95% CI: 3–33%) among kidney and pancreas transplant recipients treated with MMF and tacrolimus. These findings highlight the need for routine hematologic surveillance and early therapeutic intervention.

Paya et al. [2] reported leukopenia in 20.3% of 64 renal transplant recipients treated with MMF, tacrolimus, corticosteroids, and valganciclovir, with 7.8% experiencing severe neutropenia. Notably, a valganciclovir dose of 900 mg/day and initiation of prophylaxis on day 0 post-transplant were both significantly associated with increased leukopenia risk.

In a study on predictors of leukopenia, *Liang et al.* [3] identified significant associations with valganciclovir (HR 1.84; 95% CI: 1.25–2.70), tacrolimus (HR 3.05; 95% CI: 1.08–8.55), and ATG induction therapy. Leukopenia in this cohort was linked with increased rates of opportunistic infections and a higher frequency of immunosuppressive regimen modifications.

Rostaing et al. [4] reinforced that leukopenia typically occurs early post-transplant and is most frequently associated with valganciclovir, MMF, and calcineurin inhibitors. The severity is often dose-dependent and managed according to CTCAE grading, which guides therapeutic decisions.

Baradaran et al. [11] also documented leukopenia rates between 10–28% in patients receiving valganciclovir-based regimens, with neutropenia reaching 37.5% when co-administered with other myelotoxic agents. Identified risk factors included high cumulative doses, overlapping drug toxicity, and timing of prophylaxis initiation.

Collectively, this body of literature underscores the complex interplay of immunosuppressive and prophylactic agents in the pathogenesis of leukopenia in KT recipients. It supports the need for personalized immunosuppressive protocols, routine blood monitoring, and interdisciplinary collaboration involving nephrologists, hematologists, and infectious disease specialists. These strategies are essential to preserving graft function, reducing infection risk, and improving patient outcomes.

Materials and Methods

This narrative review was carried out through a structured search of the PubMed, Embase, and Scopus databases, focusing on articles published between January 2010 and June 2024. The search strategy employed Boolean operators and the following keywords: *"leukopenia," "neutropenia," "drug-induced," "kidney transplantation," "mycophenolate," "valganciclovir," "tacrolimus,"*

"cotrimoxazole," "immunosuppression," and *"myelosuppression."*

Inclusion criteria:

- Studies involving adult kidney transplant recipients
- Reports focusing on drug-induced leukopenia or neutropenia
- Observational studies, randomized controlled trials, case series, and systematic reviews

Exclusion criteria:

- Studies involving pediatric transplant recipients
- Leukopenia not attributed to drug-related causes (e.g., autoimmune disease, hematologic malignancies)
- Articles published in languages other than English

After initial screening and full-text assessment, nine primary 9 studies were selected for in-depth analysis. These include pivotal observational studies, retrospective cohorts, and recent reviews providing insight into the incidence, risk factors, pathophysiological mechanisms, and management approaches for drug-induced leukopenia in the context of renal transplantation.

Drug-Induced Leukopenia in Kidney Transplantation

Mycophenolate Mofetil (MMF) / Mycophenolic Acid (MPA)

Mycophenolate is one of the most commonly implicated drugs in post-transplant leukopenia. It exerts immunosuppressive effects by inhibiting inosine monophosphate dehydrogenase (IMPDH), a key enzyme in purine synthesis, thereby suppressing lymphocyte proliferation. However, this effect is not exclusive to lymphocytes and may suppress bone marrow function, leading to leukopenia and neutropenia in up to 30–40% of patients [7]. Multiple studies, including the systematic review by Raval et al. (2022) [7], identify MPA as a consistent independent risk factor for post-transplant cytopenias. Dose reduction or temporary discontinuation is the first-line approach when leukopenia occurs, although this may increase the risk of graft rejection [7].

Valganciclovir

Valganciclovir, used for cytomegalovirus (CMV) prophylaxis, is well-known for its potent myelosuppressive effects. It suppresses bone marrow by interfering with DNA synthesis in rapidly dividing cells, including neutrophil precursors. Valganciclovir-associated leukopenia typically appears within the first 3–6 months post-transplant, particularly in CMV donor-positive/recipient-negative (D+/R–) patients, often necessitating dose adjustments, temporary discontinuation, or granulocyte colony-stimulating factor (G-CSF) support [2,3].

Sulfamethoxazole-Trimethoprim (Cotrimoxazole)

Essential for Pneumocystis jirovecii pneumonia (PJP) prophylaxis, cotrimoxazole can induce leukopenia through folate antagonism and direct bone marrow suppression. It is usually implicated when administered alongside other myelosuppressive agents, especially early post-transplantation [5, 11].

Tacrolimus

Although less commonly implicated, tacrolimus has been associated with leukopenia in selected case reports and small observational studies. The exact mechanism remains unclear, but hypotheses include interference with cytokine signaling or synergistic enhancement of MPA bioavailability. A case study by Rios et al. (2024) [6] described persistent leukopenia that resolved only after switching tacrolimus to cyclosporine, highlighting tacrolimus's potential, albeit rare, myelotoxicity [6, 9].

Other Agents

- *Azathioprine* – An older agent still used in some protocols, known for dose-dependent bone marrow suppression.
- *Anti-thymocyte globulin (ATG)* – Can cause transient but severe cytopenias during the early post-induction phase.
- *Sirolimus/Everolimus* – Less frequently associated with leukopenia, but cases of pancytopenia have been reported [5, 7].

Clinical Consequences of Drug-Induced Leukopenia

Drug-induced leukopenia and neutropenia in kidney transplant recipients carry significant clinical implications. These hematologic abnormalities increase susceptibility to opportunistic infections, including CMV, Pneumocystis jirovecii pneumonia, BK virus nephropathy, and fungal infections. The incidence and severity of infections correlate with the degree and duration of neutropenia [3, 7].

Leukopenia often necessitates modification of immunosuppressive or prophylactic regimens, including dose reduction, temporary discontinuation, or complete cessation of the offending agent. However, these interventions risk under-immunosuppression, which may lead to acute rejection, thereby compromising graft function and patient outcomes [4, 7].

From a healthcare system perspective, leukopenia contributes to prolonged hospitalizations, increased outpatient monitoring, greater use of supportive therapies such as G-CSF, and frequent consultations with hematology and infectious disease specialists. These factors collectively increase healthcare costs and burden for patients and transplant teams [5, 10].

Management Strategies

The management of drug-induced leukopenia in kidney transplant recipients requires a careful, individualized approach that balances effective immunosuppression against the risks of infection and hematologic toxicity.

Key management strategies include:

- Routine monitoring of complete blood count (CBC) with differential, particularly during the first six months post-transplant when risk is highest [2, 4].

- Identification of the causative agent, considering temporal associations between drug initiation and onset of cytopenia [7].
- Stepwise therapy modification, often beginning with dose reduction or discontinuation of:
  - Mycophenolate mofetil (MMF) or mycophenolic acid (MPA)
  - Valganciclovir
  - Trimethoprim-sulfamethoxazole
  - Less commonly, tacrolimus, azathioprine, or mTOR inhibitors
- Supportive treatment with G-CSF (e.g., filgrastim) for moderate to severe neutropenia (absolute neutrophil count <1000/μL), particularly in cases with active infection or high immunologic risk [7, 10].
- Infectious disease evaluation and adjustment of prophylaxis according to leukopenia severity and expected duration [3, 11, 12].
- Bone marrow biopsy may be warranted in refractory or unclear cases to exclude alternative marrow pathology [5].

An interdisciplinary team including nephrologists, hematologists, and infectious disease specialists is essential for optimal management.

Clinical Illustration (Case Report)

To illustrate the complexity of diagnosing and managing drug-induced leukopenia in clinical practice, we report the case of a 36-year-old male patient with end-stage renal disease who underwent living donor kidney transplantation. Preoperative hematologic parameters were within normal limits, and no induction immunosuppression was administered. The patient received a maintenance immunosuppressive regimen consisting of MPA, tacrolimus, corticosteroids, and valganciclovir for CMV prophylaxis.

Two months post-transplant, he developed leukopenia (WBC: 1400/μL) and neutropenia (ANC: 700/μL), while renal function remained suboptimal (creatinine: 1.82 mg/dL). Virological screening was negative, ruling out CMV or BK virus reactivation. Medication-induced leukopenia was suspected. A multidisciplinary team-initiated tapering of potentially myelotoxic drugs, and granulocyte colony-stimulating factor (G-CSF; filgrastim) therapy was introduced.

Neutrophil counts improved progressively following G-CSF initiation, and tacrolimus dosing was adjusted based on therapeutic drug monitoring (level: 3.1 ng/mL). White blood cell counts normalized within two weeks (WBC: 5400/μL) and remained stable throughout an 11-month follow-up period without infectious complications or evidence of rejection.

This case underscores the importance of timely identification and modification of leukopenia-inducing agents, as well as the effectiveness of supportive strategies like G-CSF. It also reflects the real-world complexity of balancing infection risk with under-immunosuppression in the early post-transplant period.

Discussion

Drug-induced leukopenia (DIL) remains a significant complication following kidney transplantation, with important diagnostic and therapeutic implications. The literature consistently identifies mycophenolate mofetil (MMF), valganciclovir, and cotrimoxazole as the primary agents responsible for leukopenia in this patient population, while tacrolimus is occasionally implicated in rare or refractory cases. The multifactorial etiology of DIL—encompassing direct myelotoxicity and synergistic drug interactions—complicates clinical management and necessitates a nuanced, patient-centered approach tailored to individual risk profiles.

Several studies, including those by Raval et al. [7] and Khalil et al. [5], emphasize the high incidence of leukopenia during the early post-transplant period, particularly among CMV serostatus D+/R– recipients receiving MMF and valganciclovir [1, 2]. This subgroup appears especially vulnerable to profound neutropenia, likely due to the combined myelosuppressive effects of immunosuppressive and antiviral agents. Mechanistically, MMF inhibits inosine monophosphate dehydrogenase (IMPDH), impairing purine synthesis, while valganciclovir interferes with DNA replication—both targeting rapidly proliferating hematopoietic precursors.

The role of tacrolimus remains less well defined. While traditionally considered non-myelosuppressive, case reports such as that by Rios et al. suggest tacrolimus may contribute to leukopenia via indirect mechanisms, including cytokine modulation or potentiation of MMF toxicity [3]. These observations highlight the need for heightened vigilance when evaluating persistent cytopenias in patients receiving complex immunosuppressive regimens.

Clinically, leukopenia presents a therapeutic challenge: dose reductions or discontinuation of implicated agents may reduce infection risk but increase the likelihood of under-immunosuppression and acute rejection episodes. This necessitates a careful, stepwise approach to therapy modification and often requires multidisciplinary input from nephrologists, hematologists, and infectious disease specialists.

Moreover, the frequent use of G-CSF, increased infection rates, and prolonged hospitalizations underscore the substantial healthcare burden associated with DIL. Implementation of structured hematologic monitoring protocols, especially within the first six months post-transplant, is critical for early detection and timely intervention.

Importantly, standardized guidelines for the management of DIL remain lacking. Most current practices rely on expert consensus, small cohort studies, or institutional experience, revealing a significant gap in evidence-based recommendations. This gap highlights the

urgent need for prospective multicenter trials to establish optimal management protocols.

Ultimately, the effective management of DIL requires a personalized, risk-adapted strategy that considers patient-specific factors such as CMV serostatus, immunological risk, and pharmacogenetic variability. Given the increasing complexity of post-transplant pharmacotherapy, future research should focus on identifying predictive biomarkers and developing approaches to minimize hematologic toxicity without compromising graft survival.

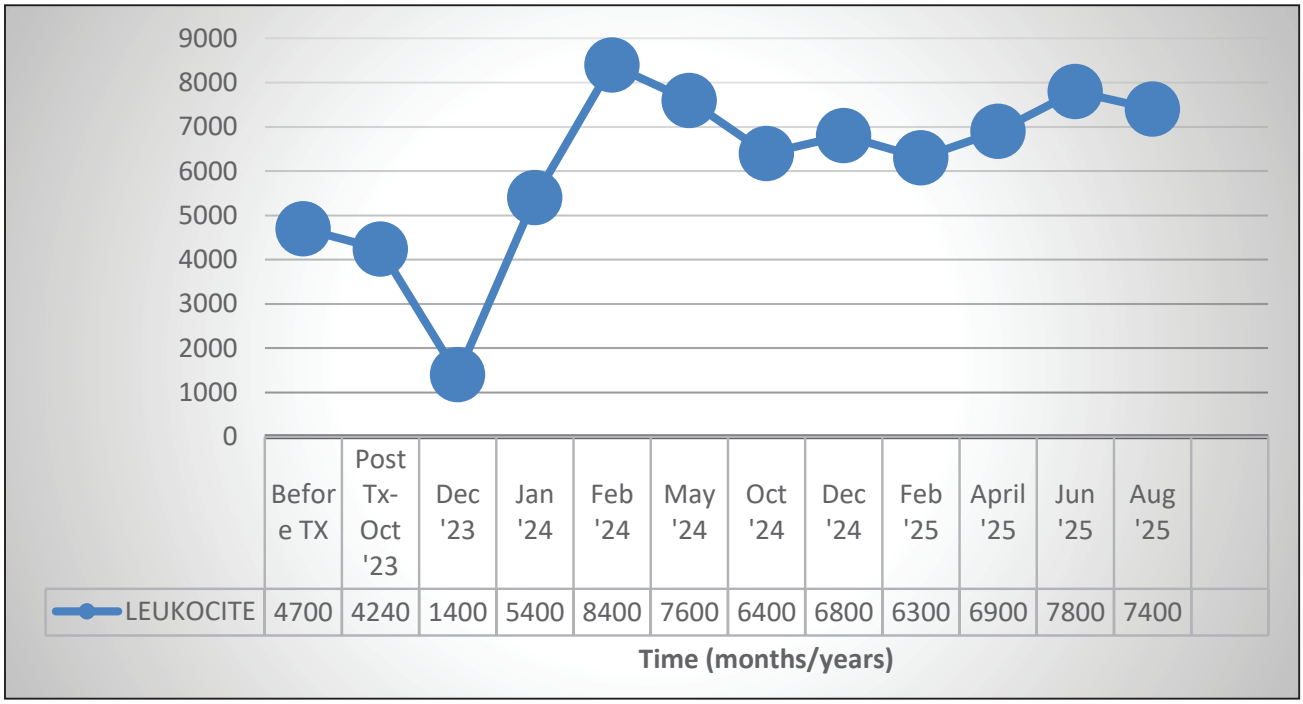

Figure 1. Leukocyte (WBC) counts (cells/μL) were measured before transplantation and at multiple time points from October 2023 to August 2025.

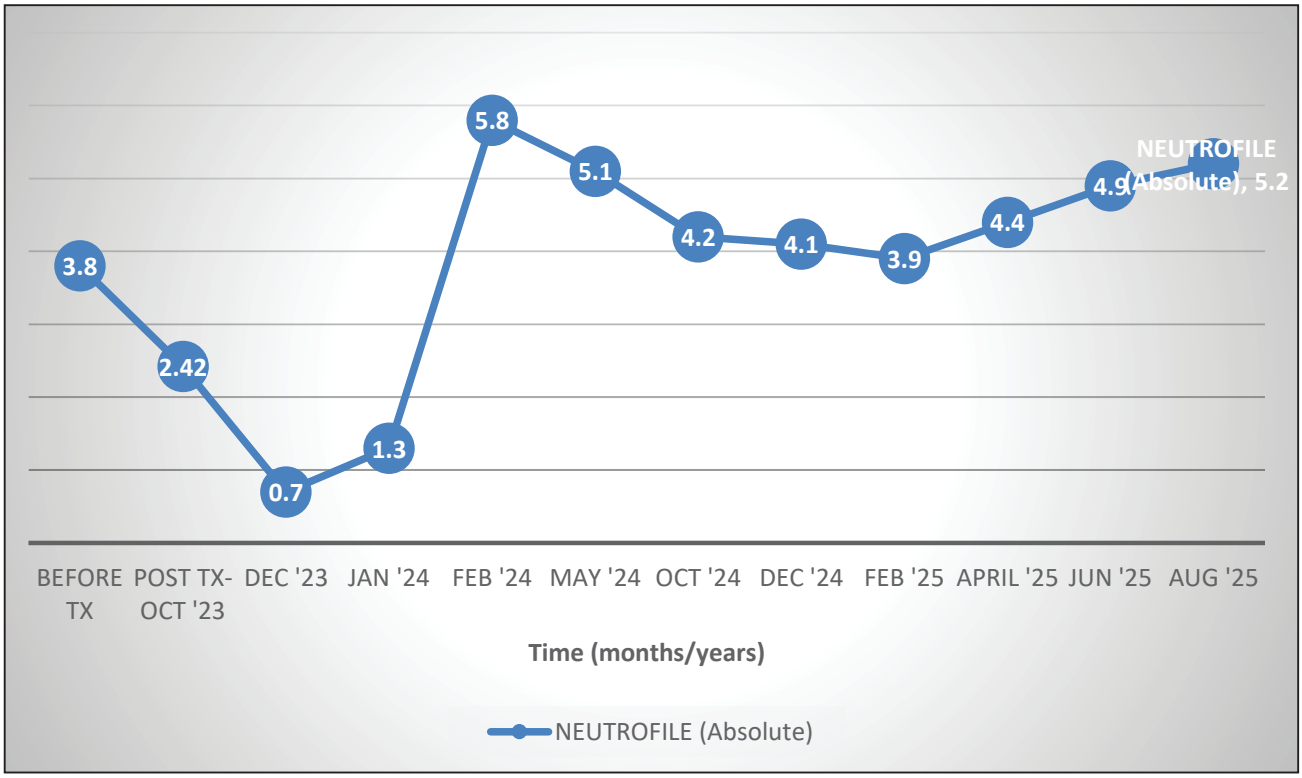

Figure 2. Absolute neutrophil counts (×10⁹/L) measured before transplantation and at multiple time points after transplantation from October 2023 to August 2025.

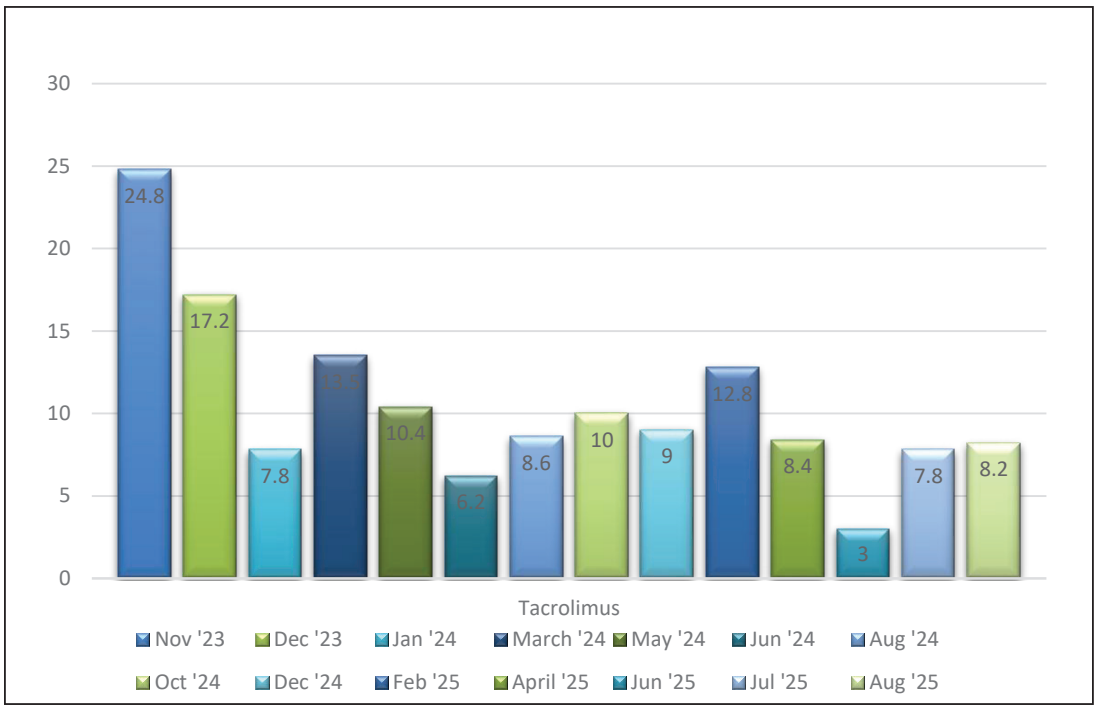

Figure 3. Tacrolimus levels (ng/mL) were measured at periodic intervals from November 2023 to August 2025.

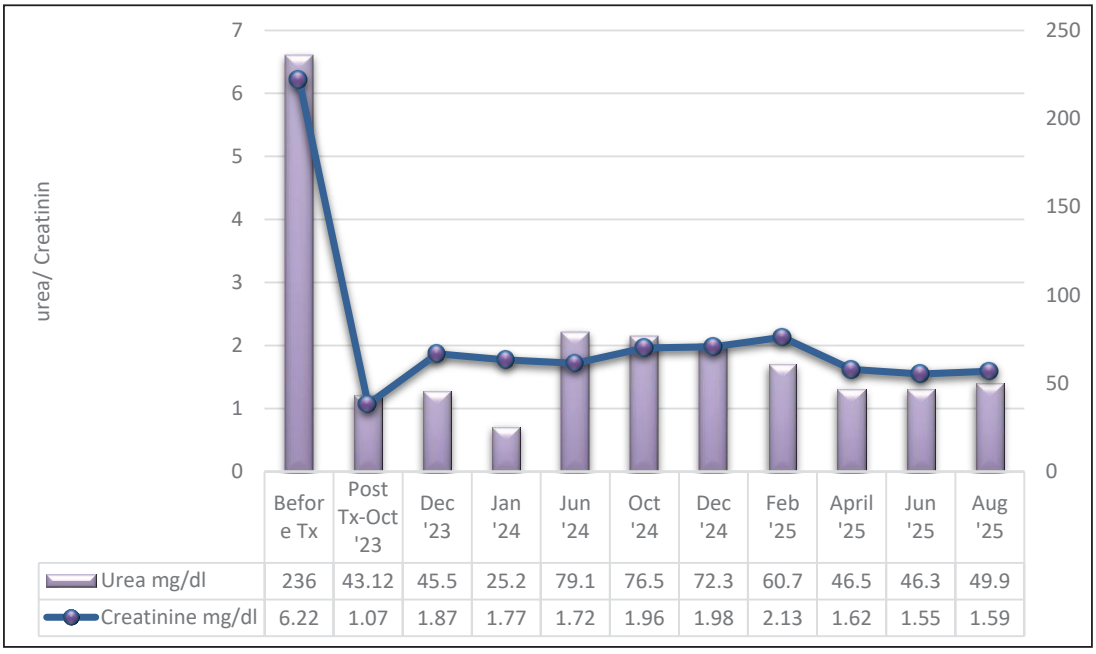

Figure 4. Serum urea (mg/dL) and creatinine (mg/dL) levels were measured before transplantation and at multiple time points after transplantation from October 2023 to August 2025.

Conclusion

Drug-induced leukopenia is a prevalent and clinically significant complication in kidney transplant recipients. Mycophenolate mofetil and valganciclovir remain the most frequent causative agents, while cotrimoxazole and tacrolimus may also contribute under specific clinical circumstances. The management of DIL is inherently complex, requiring a delicate balance between maintaining adequate immunosuppression and preventing infectious complications.

Early recognition, regular hematologic monitoring, and individualized modification of immunosuppressive and prophylactic regimens are essential to optimizing patient outcomes. Despite its frequency, the absence of standardized management protocols for DIL highlights the need for robust prospective studies to inform clinical practice.

Going forward, interdisciplinary collaboration and

a patient-centered approach will be vital to minimizing hematologic toxicity in kidney transplant pharmacotherapy while preserving long-term graft function and patient survival.

Abbreviations

KT - Kidney Transplant; MMF - Mycophenolate Mofetil; TMP-SMX - Trimethoprim-Sulfamethoxazole; DIL - Drug-Induced Leukopenia; ATG - Antithymocyte Globulin; G-CSF - Granulocyte Colony-Stimulating Factor; MPA - Mycophenolic Acid;CMV - Cytomegalovirus; PJP - Pneumocystis Jirovecii Pneumonia; CBC - Complete Blood Count; IMPDH - Inosine Monophosphate Dehydrogenase.

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Patient Consent: Written informed consent was obtained from the patient for publication of this case report and the accompanying clinical data and figures.

References

1. Gujral, N., Freeman, H. J., & Thomson, A. B. (2012). Celiac disease: prevalence, diagnosis, pathogenesis, and treatment. World journal of gastroenterology, 18(42), 6036–6059. https://doi.org/10.3748/wjg.v18.i42.6036
2. Paya, C., Humar, A., Dominguez, E., Washburn, K., Blumberg, E., Alexander, B., Freeman, R., Heaton, N., Pescovitz, M. D., & Valganciclovir Solid Organ Transplant Study Group (2004). Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 4(4), 611–620. https://doi.org/10.1111/j.1600-6143.2004.00382.x
3. Liang X, Famure O, Li Y, Kim SJ. Incidence and Risk Factors for Leukopenia in Kidney Transplant Recipients Receiving Valganciclovir for Cytomegalovirus Prophylaxis. Progress in Transplantation. 2018;28(2):124-133. doi:10.1177/1526924818765798
4. Rostaing, L., Jouve, T., Terrec, F., Malvezzi, P., & Noble, J. (2023). Adverse Drug Events after Kidney Transplantation. Journal of personalized medicine, 13(12), 1706. https://doi.org/10.3390/jpm13121706
5. Khalil K, Shapiro R, Jordan ML. Hematologic toxicities after renal transplantation: a comprehensive review. Transplant Rev (Orlando). 2018;32(1):58–67.
6. Rios JP, Mead LC. Tacrolimus-induced leukopenia: a case report and review of the literature. Clin Transplant. 2024;38(1):e14792.
7. Raval A, Patel H, Gill J. Drug-induced neutropenia in kidney transplantation: a systematic review. Nephrol Dial Transplant. 2022;37(6):1094–103.
8. De Rycke, A., Dierickx, D., & Kuypers, D. R. (2011). Tacrolimus-induced neutropenia in renal transplant recipients. Clinical journal of the American Society of Nephrology: CJASN, 6(3), 690–694. https://doi.org/10.2215/CJN.07320810
9. Zafrani, L., Truffaut, L., Kreis, H., Etienne, D., Rafat, C., Lechaton, S., Anglicheau, D., Zuber, J., Ciroldi, M., Thervet, E., Snanoudj, R., Mamzer, M. F., Martinez, F., Timsit, M. O., Bergougnoux, L., & Legendre, C. (2009). Incidence, risk factors, and clinical consequences of neutropenia following kidney transplantation: a retrospective study. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 9(8), 1816–1825. https://doi.org/10.1111/j.1600-6143.2009.02699.x
10. Datrino, L. N., Boccuzzi, M. L., Silva, R. M., Castilho, P. H. B. T., Riva, W. J., Rocha, J. S., & Tustumi, F. (2024). Safety and Efficacy of Mycophenolate Mofetil Associated With Tacrolimus for Kidney-pancreas and Kidney Transplantation: A Systematic Review and Meta-Analysis of Randomized Studies. Transplantation proceedings, 56(5), 1066–1076. https://doi.org/10.1016/j.transproceed.2024.05.014
11. Lee, A. Y., Jeong, J., Heo, K. N., Park, S., Ah, Y. M., Han, J. M., Lee, J. Y., & Min, S. I. (2025). Complications Associated with Immunosuppressive Agents in Solid Organ Transplant Recipients: A Nationwide Analysis. Journal of Clinical Medicine, 14(10), 3602. https://doi.org/10.3390/jcm14103602
12. Dogjani, A., Vassiliu, P., Georgiou, C., et al. (2025). The 9th Albanian Congress of Trauma and Emergency Surgery. Albanian Journal of Trauma and Emergency Surgery, 9(2.9), 1-159. https://doi.org/10.32391/ajtes.v9i2.9.508