Concurrent Trimethoprim-Sulfamethoxazole Induced Immune Hemolytic Anemia and Thrombocytopenia Following Allogeneic Stem Cell Transplant

Edison W. Tsui MD[1], Andrea N. Gero[2], Yevgeniy A. Linnik MD[3], Isabella W. Martin MD[3], Zbigniew M. Szczepiorkowski MD[1,3], John M. Hill, Jr MD[1,4] and Nancy M. Dunbar MD[1,3]

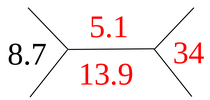
1. Department of Hematology/Oncology, Dartmouth-Hitchcock Medical Center, Lebanon, NH; 2. Geisel School of Medicine at Dartmouth, Hanover, NH; 3. Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, NH; 4. Blood and Marrow Transplant Program, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH

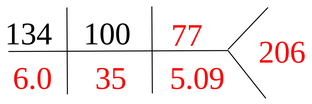
Introduction

Drug-induced immune hemolytic anemia (DIIHA) and drug-induced immune thrombocytopenia (DIIT) are rare but dangerous complications of pharmacotherapy which may be under-recognized in hematopoietic stem cell transplant (HSCT) patients due to overlap of other medication effects and post-transplant complications.

Patient Presentation

A 61 year old female with NK cell deficiency and GATA-2 associated myelodysplastic syndrome s/p allogeneic HSCT (day +58) presented with 3 days of severe back pain, muscle cramps, and dark urine. Her medications were notable for Acyclovir, Tacrolimus, and Trimethoprim-Sulfamethoxazole (TMP-SMX). On assessment she was found to be febrile (38.3°C) with scleral icterus, bilateral upper and lower extremity edema, an erythematous maculopapular rash and oliguria. She was admitted for further evaluation and management.





Presenting Labs	
LDH	2500 [110-220 unit/L]
ALT	97 [0-30 unit/L]
AST	271 [0-30 unit/L]
Tbili/Direct	2.7/1.1 [0.2-1.3 mg/dL]
Alk Phos	232 [40-104 unit/L]
Haptoglobin	22 [30-200 mg/dL]
Uric Acid	11.8 [2.5-6.5 mg/dL]
D-Dimer	3896 [0-500 FEU ng/ml]
Fibrinogen	320 [175-450 mg/dL]

Clinical Course

Patient received 2 units of pRBCs and underwent dialysis before receiving a renal biopsy. Given the near absence of schistocytes, this made TTP-HUS less likely **(Figure 1)**. The presence of possible cold agglutination and the positive direct antibody test (DAT) raised suspicion for cold autoimmune hemolytic anemia. One dose of Rituximab was given on hospital day 2. An initial assay demonstrated a strongly positive DAT with polyspecific reagent and C3, however, a cold antibody screen was only positive for anti-I at 4°C. The patient underwent a renal biopsy **(Figure 1)**. After further review, the possibility of drug-mediated process was raised and no further Rituximab was given. With Tacrolimus and TMP-SMX deemed the most likely mediators, samples of patient serum and drugs obtained from the patient's pharmacy were sent to a reference laboratory for further testing.

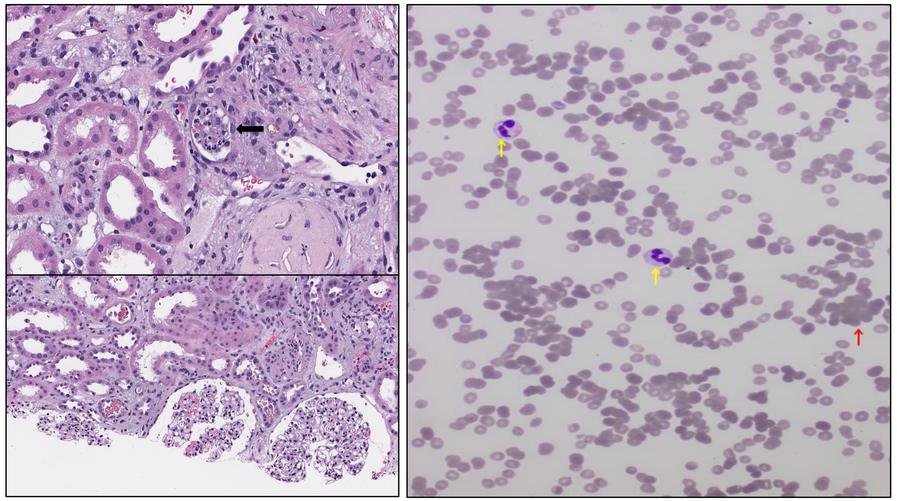


Figure 1. Left Top: Kidney biopsy demonstrating acute tubular injury with sloughing of tubular epithelium, most suggestive of toxic type etiology. Left Bottom: Scattered pigmented casts most likely representing free Hgb casts. Right: Peripheral blood smear at 10x magnification demonstrating marked hyperchromia, borderline macrocytic anemia, and thrombocytopenia. Red arrow denotes erythrocyte clumping, yellow arrows denote toxic granulations.

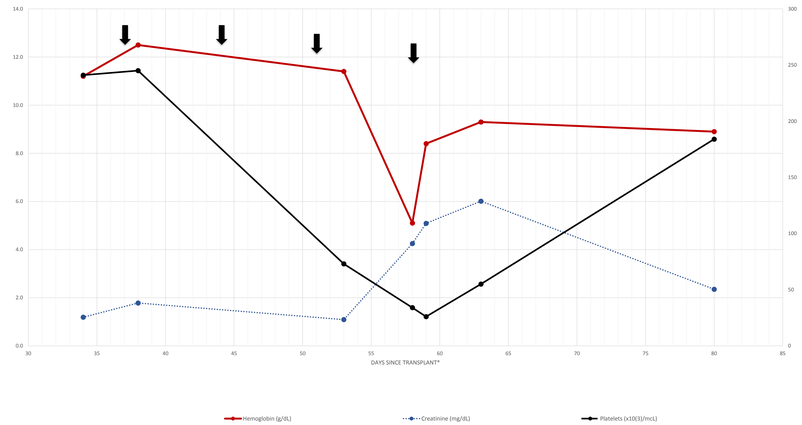


Figure 2. TMP-SMX had been prescribed on a weekend dose schedule with doses received on post transplant days +36, +43, +50, and +57 (black arrows) prior to admission. Tacrolimus on a twice daily dose schedule had been taken since day -2 of transplant. Both TMP-SMX and Tacrolimus were held on admission.

*Note Day 0 = Day of Transplant.

Patient Follow-Up

During the patient's hospital course, TMP-SMX and Tacrolimus continued to be held pending appropriate renal recovery. Her clinical and laboratory status improved with continued hemodialysis and a brief course of steroids. She was discharged home after 15 days in stable condition. A trend of the patient's hemoglobin, platelets, and creatinine are depicted in **Figure 2**.

Drug-dependent antibody testing with TMP-SMX and Tacrolimus resulted 3-days prior to when the patient was scheduled to restart her medications. Mixing the patient's serum with TMP-SMX revealed drug-antibody immune complexes to RBCs. Further testing with platelets also revealed TMP-SMX-induced platelet antibodies. This was consistent with drug-induced immune hemolytic anemia and drug-induced immune thrombocytopenia.

Discussion/Conclusion

DIIHA and DIIT are rare and potentially fatal complications of pharmacotherapy. To date, the literature reports 7 and 50 cases of each, respectively, with no reported cases of concurrent hemolytic anemia and thrombocytopenia due to TMP-SMX use.[1-5] TMP-SMX is one of the most commonly used agents in the world and is often the first line treatment for PJP prophylaxis in immunosuppressed patients following HSCT. It is generally well tolerated both in its recommended thrice weekly regimen and in its alternate regimen of weekend administration only.[6-8]

This case illustrates the fact that concomitant occurrence of both DIIHA and DIIT is rare and can present a diagnostic challenge in the setting of polypharmacy, utilization of intermittent medication (weekend only) dosing and a complicated clinical scenario with many potential drug sequelae. More specifically, it highlights the difficulty in assessing the cause of hemolysis and thrombocytopenia in HSCT patients, where overlap of signs and symptoms with other potential comorbidities makes clinical suspicion for this rare entity quite low. Hopefully, presentation of this case will encourage providers to consider this potential diagnosis when the appropriate clinical scenario is encountered.

REFERENCES

1. Aster RH, Curtis BR, McFarland JG, et al. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost 2009;7:911-8. 8.
2. Herrington A, Mahmood A, Berger R. Treatment options in sulfamethoxazole-trimethoprim-induced thrombocytopenic purpura. South Med J 1994;87:948-50. 9.
3. Kiefel V, Santoso S, Schmidt S, et al. Metabolite-specific (IgG) and drug-specific antibodies (IgG, IgM) in two cases of trimethoprim-sulfamethoxazole-induced immune thrombo-cytopenia. Transfusion 1987;27:262-5. 10.
4. Abu-Elmagd KM, Bronsther O, Kobayashi M, et al. Acute hemolytic anemia in liver and bone marrow transplant patients under FK 506 therapy. Transplant Proc 1991;23:3190-2. 11.
5. DiGiuseppe JA, Bastacky SI, Shirey RS, et al. Tacrolimus-related posttransplant lymphoproliferative disorder presenting as autoimmune hemolytic anemia. Arch Pathol Lab Med 1996;120:282-5.
6. Tuan IZ, Dennison D, Weisdorf DJ. Pneumocystis carinii pneumonitis following bone marrow transplantation. Bone Marrow Transplant 1992;10:267-72. 19.
7. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for pre-venting infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143-238.
8. Munoz P, Munoz RM, Palomo J, et al. Pneumocystis carinii infection in heart transplant recipients. Efficacy of a weekend prophylaxis schedule. Medicine (Baltimore) 1997;76:415-22. 21.