Drug-Induced Thrombocytopenia in an Immunosuppressed Renal Transplant Recipient: A Diagnostic and Therapeutic Challenge

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ABSTRACT

Introduction: Drug-induced thrombocytopenia (DITP) is a rare but life-threatening disorder, particularly in immunosuppressed patients; it can occur via immune and nonimmune mechanisms. β-lactam antibiotics are infrequently known to cause immune DITP.

Case Presentation: We present the case of a 30-year-old woman with a history of renal transplantation who developed severe thrombocytopenia while receiving ganciclovir for cytomegalovirus, and meropenem and cefoperazone/sulbactam for sepsis. Despite discontinuing ganciclovir, she developed thrombocytopenia, which worsened upon switching to cefoperazone. Her platelet count improved only after discontinuing both β-lactam antibiotics and the administration of eltrombopag.

Discussion: While ganciclovir is a well-known myelosuppressive agent, β-lactam antibiotics such as meropenem and cefoperazone have also been implicated in DITP, particularly via immune-mediated mechanisms. Similar case reports are limited, especially involving immunosuppressed patients requiring complex antimicrobial regimens.

Conclusions: Clinicians should monitor patients receiving antibiotics for DITP, particularly those on immunosuppressive therapy. This case underscores the need for close monitoring, early drug discontinuation, and consideration of thrombopoietin receptor agents in severe cases of DITP.

INTRODUCTION

Thrombocytopenia, defined as a platelet count of less than 150 000/μL, can result from multiple causes, including bone marrow suppression and increased platelet destruction. Drug-induced thrombocytopenia (DITP) is a well-known phenomenon[1] often associated with certain medications, particularly those affecting hematological function. This case describes a patient with DITP that persisted following discontinuation of the suspected agent. We aim to highlight the importance of monitoring platelet counts in patients receiving antibiotics with potential hematological toxicity and the significance of drug interactions in managing complex clinical scenarios involving immunosuppressed patients.

CASE PRESENTATION

A 30-year-old woman with a history of renal transplant 7 years prior was admitted to the hospital for recurrent diarrhea (8 to 10 daily episodes of watery, nonbloody stool), with the most recent episode 2 days prior. She had been hospitalized 2 weeks earlier for a similar complaint; at that time, the workup was negative except for cytomegalovirus (CMV) polymerase chain reaction (PCR) of 200 copies/mL. A colonoscopy performed nearly 6 months earlier was unremarkable. Following her previous discharge, she started oral valganciclovir. Additional medications included tacrolimus (1.5 mg twice daily), mycophenolate mofetil (500 mg twice daily), and oral prednisone (5 mg daily).

On physical examination, blood pressure was 90/50 mm Hg, heart rate was 100 beats per minute, and oxygen saturation was 98% on room air. Her weight was approximately 40 kg. She appeared hypovolemic with dry tongue and reduced skin turgor; jugular venous pressure was normal. The chest was clear to auscultation, heart sounds were normal, the abdomen was soft and nontender, and there was no peripheral edema.

Her initial laboratory tests showed a hemoglobin level of 10.0 g/dL, white blood cell count (WBC) count of 7700/μL, and a platelet count of 155 000/μL. Chemistry panel revealed

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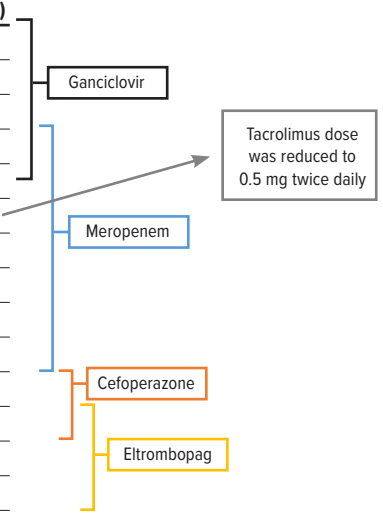
urea, 128 mg/dL; creatinine, 8.1 mg/dL; sodium, 132 mmol/L; potassium, 2.8 mmol/L, chloride, 112 mEq/L; and bicarbonate, 8 mEq/L. An extensive workup for diarrhea – including stool examination for *Clostridium difficile* toxin, *Cryptosporidium*, and *Isospora* – was negative. She received hydration with Ringer lactate containing bicarbonate and potassium supplementation and was switched to a renally adjusted dose of intravenous ganciclovir. Mycophenolate mofetil was discontinued.

Figure. Trend of Complete Blood Cell Count and Medication Use

Days Since Admission	Hemoglobin (g/dlL	WBC ($x10^3/\mu L$)	Platelets ($x10^3/\mu L$)
Day 1	10.6	7.7	155
Day 8	9.5	3.3	127
Day 10	7.8	2.4	140
Day 11	5.4	1	98
Day 12	7.4	1.1	71
Day 13	9.3	0.8	75
Day 14	9.9	0.5	60
Day 15	10.2	0.67	40
Day 16	9.8	0.69	35
Day 17	8.7	0.8	23
Patient was discharged at her request			
Day 20	9.1	6.5	6
Day 23	8.9	10.7	80
Day 25	8.3	6.8	80
Day 31			128



Hospital Course

The patient's electrolytes and acid-base balance were corrected over the next few days, and diarrhea improved after 6 days. Her creatinine level improved to 2.2 mg/dL. However, she developed a significant decline in WBC and platelet counts on hospital day 10, prompting discontinuation of ganciclovir. She received filgastrim for severe leukopenia; while the WBC count stabilized, the platelet count continued to decline (Figure). Filgastrim was discontinued after 7 days. A workup for alternate causes of bicytopenia – including repeat CMV PCR, parvovirus, Epstein Barr virus, blood and urine cultures, B12, folic acid, tacrolimus trough, beta-D-glucan, galactomannan, and a peripheral blood smear for schistocytes, lactate dehydrogenase, and haptoglobin – was inconclusive. However, urine culture grew *Escherichia coli*, and tacrolimus trough was elevated at 14.1 ng/mL, prompting a dose reduction. She was started on meropenem but her platelet count fell to 23 000/μL. She was then switched to cefoperazone/sulbactam and discharged at her request with follow-up in 3 days.

Cefoperazone/sulbactam was discontinued 3 days later when her platelet count reached 6000/μL. She was transfused with 1 apheresis unit of platelets and started on eltrombopag. Her platelet count subsequently improved to 80 000/μL (Figure). Eltrombopag was discontinued after 7 days, and the platelet count continued to rise to 128 000/μL. Renal function normalized during follow-up.

DISCUSSION

DITP is a rare side effect caused by drug-dependent antibodies that react with platelet membrane glycoproteins only when the implicated drug is present.[2] It typically occurs 1 to 2 weeks after beginning a new drug or suddenly after a single dose of a medication previously taken intermittently. However, severe thrombocytopenia can occur immediately after the first administration of antithrombotic agents such as abciximab, tirofiban, and eptifibatide. Recovery from DITP usually begins within 1 to 2 days of drug cessation and is typically complete within a week.1 Immune and nonimmune mechanisms can cause DITP, including impaired maturation or replication of megakaryocytes and reduced release of platelets from the bone marrow. Where an immune mechanism is involved, an increased rate of apoptosis or increased peripheral destruction of platelets is implicated, and antibodies specific to individual drug structures have been identified.[3]

Ganciclovir is associated with bone marrow suppression – including neutropenia and thrombocytopenia[4] – with reported thrombocytopenia rates of approximately 23%.[5] Despite stopping ganciclovir and later switching from meropenem to cefoperazone, this patient's platelet count reached a nadir of 6000/μL on hospital day 20. This extreme thrombocytopenia, occurring after discontinuation of the primary myelosuppressive agent, implicated the beta-lactam antibiotics as likely culprits in immune-mediated DITP. Platelet recovery occurred only after both meropenem and cefoperazone were discontinued. Alternative causes of thrombocytopenia, including CMV, Epstein Barr virus, parvovirus, and thrombotic microangiopathy (TMA), were ruled out. The patient was also on tacrolimus, which can cause thrombocytopenia primarily via thrombotic microangiopathy.[6,7] While the tacrolimus level was 14 mg/dL, the absence of clinical and laboratory features of TMA and recovery of platelets while remaining on a (reduced) dose of tacrolimus make it an unlikely cause.

DITP typically results from drug-dependent antibodies that recognize platelet glycoproteins only in the presence of the drug. These antibodies trigger platelet destruction through complement activation or phagocytosis. The diagnosis is supported by the time course of thrombocytopenia and its resolution

upon drug discontinuation.[1] In this patient, thrombocytopenia resolved after discontinuing all suspected drugs, supporting the diagnosis of DITP but making it difficult to pinpoint a single causative agent.

Six types of antibiotics have been identified according to their antibody-binding mechanisms.[2] While meropenem and cefoperazone/sulbactam have not been specifically classified into one of these 6 categories, they likely follow the "hapten-dependent" mechanism similar to other penicillins, where drugs covalently link to cell surface proteins to induce a drug-specific immune response.[2] DITP due to myelosuppression is also a possibility; however, the decrease of platelet production via myelosuppression tends to develop gradually and after at least 10 days of antimicrobial therapy. In contrast, immune-mediated thrombocytopenia could present earlier, primarily after 7 to 14 days.[8] Our patient developed DITP after 4 to 5 days after administration of the drug, suggesting an immune-mediated mechanism rather than myelosuppression.

Meropenem has been reported to cause DITP more frequently than other drugs; one study found that it caused thrombocytopenia in 37.81% of renally compromised patients.[9] It is also known cause of drug-induced pancytopenia and neutropenia.[10,11] Cefoperazone has also been documented to cause coagulation disorders: one study reported an incidence of 9.2% in patients receiving cefoperazone,[12] while another reported a DITP incidence of 2.4% in patients on cefoperazone.[13]

While in most cases of drug-induced thrombocytopenia, cessation of treatment is sufficient for reversal of a low platelet count, in our case, the patient was given eltrombopag to increase the platelet count. Eltrombopag is usually used to treat chronic immune thrombocytopenia;[14] however, its usefulness in treating chemotherapy-induced thrombocytopenia[15] suggests it may also be useful to treat patients with DITP, as seen in our case.

CONCLUSIONS

This case highlights the importance of recognizing DITP, particularly in immunosuppressed patients receiving multiple medications. Beta-lactam antibiotics can induce severe immune-mediated thrombocytopenia in rare instances. Prompt identification and discontinuation of the offending agent are crucial. Additionally, the use of eltrombopag in severe DITP warrants further exploration as a potential therapeutic intervention.

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REFERENCES

1. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. *Hematology Am Soc Hematol Educ Program*. 2009;153-158. doi:10.1182/asheducation-2009.1.153

2. Curtis BR. Drug-induced immune thrombocytopenia: incidence, clinical features, laboratory testing, and pathogenic mechanisms. *Immunohematology*. 2014;30(2):55-65.

3. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *J Thromb Haemost.* 2009;7(6):911-918. doi:10.1111/j.1538-7836.2009.03360.x

4. Matsumoto K, Shigemi A, Ikawa K, et al. Risk factors for ganciclovir-induced thrombocytopenia and leukopenia. *Biol Pharm Bull*. 2015;38(2):235-238. doi:10.1248/bpb.b14-00588

5. Khalil MAM, Khalil MAU, Khan TFT, Tan J. Drug-induced hematological cytopenia in kidney transplantation and the challenges it poses for kidney transplant physicians. *J Transplant.* 2018;2018:9429265. doi:10.1155/2018/9429265

6. Chin JL, Hisamuddin SH, O'Sullivan A, Chan G, McCormick PA. Thrombocytopenia, platelet transfusion, and outcome following liver transplantation. *Clin Appl Thromb Hemost.* 2016;22(4):351-360. doi:10.1177/1076029614559771

7. Boyer NL, Niven A, Edelman J. Tacrolimus-associated thrombotic microangiopathy in a lung transplant recipient. *BMJ Case Rep.* 2013;2013:bcr2012007351. doi:10.1136/bcr-2012-007351

8. Loo AS, Gerzenshtein L, Ison MG. Antimicrobial drug-induced thrombocytopenia: a review of the literature. *Semin Thromb Hemost.* 2012;38(8):818-829. doi:10.1055/s-0032-1328882

9. Khan MU, Yousuf RI, Shoaib MH. Drug utilization evaluation of meropenem and correlation of side effects with renal status of patients in a teaching based hospital. *Pak J Pharm Sci.* 2014;27(5 Spec no):1503-1508.

10. Van Tuyl JS, Jones AN, Johnson PN. Meropenem-induced neutropenia in a neonate. *J Pediatr Pharmacol Ther.* 2016;21(4):353-357. doi:10.5863/1551-6776-21.4.353

11. Hussain K, Salat MS, Mohammad N, et al. Meropenem-induced pancytopenia in a preterm neonate: a case report. *J Med Case Rep.* 2021;15(1):25. doi:10.1186/s13256-020-02632-1

12. Wang W, Liu Y, Yu C, et al. Cefoperazone-sulbactam and risk of coagulation disorders or bleeding: a retrospective cohort study. *Expert Opin Drug Saf.* 2020;19(3):339-347. doi:10.1080/14740338.2020.1713090

13. Zhu B, Jin P, Li J, Zhu Y. Retrospective analysis of risk factors for cefoperazone/sulbactam-induced thrombocytopenia in adult Chinese patients: a six-year real-world study. *Infect Drug Resist.* 2024;17:3901-3911. doi:10.2147/IDR.S475590

14. Elgebaly AS, Ashal GE, Elfil M, Menshawy A. Tolerability and efficacy of eltrombopag in chronic immune thrombocytopenia: meta-analysis of randomized controlled trials. *Clin Appl Thromb Hemost*. 2017;23(8):928-937. doi:10.1177/1076029616663849

15. Gurumurthy G, Kisiel F, Gurumurthy S, Gurumurthy J. Role of thrombopoietin receptor agonists in chemotherapy-induced thrombocytopenia: a meta-analysis. *J Oncol Pharm Pract.* 2025;31(1):4-11. doi:10.1177/10781552231219003

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