

Nephrotoxicity Associated with Low-dose Methotrexate and Outpatient Parenteral Microbial Therapy: A Case Report, Review of the Literature and Pathophysiologic Insights

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Abstract Methotrexate (MTX) toxicity can affect multiple organ systems, manifesting as nephrotoxicity, myelosuppression, hepatotoxicity, mucositis, and gastrointestinal upset. Serious adverse events are rare in patients prescribed low-dose methotrexate. We present a case of an 86-year-old female on a weekly dose of oral MTX 12.5 mg for rheumatoid arthritis presenting with painful gingiva and oral bleeding during outpatient antimicrobial therapy (OPAT) for osteomyelitis with vancomycin and piperacillin-tazobactam. She had acute kidney injury (AKI), elevated serum MTX levels, thrombocytopenia, neutropenia, and a vancomycin level three times therapeutic concentration. MTX toxicity was suspected to have been triggered by vancomycin and piperacillin-tazobactam causing AKI and impaired renal clearance of MTX which itself is nephrotoxic. The patient was managed with leucovorin, alkalinized intravenous fluids, and filgrastim injections over a 2-week period. Her renal function continued to be reduced at 5-week outpatient follow-up, far after other markers of toxicity normalized. This case demonstrates the importance of considering potential drug-drug interactions and the need for robust monitoring for OPAT in select groups.

Keywords: outpatient parenteral antimicrobial therapy, anti-folate, methotrexate, nephrotoxicity, monitoring, surveillance

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1. Introduction

Outpatient parenteral antimicrobial therapy (OPAT) is a cost-saving alternative to hospitalization in the management of stable patients with infections that require prolonged antibiotic therapy [1]. OPAT was initially used in the 1970s for children with cystic fibrosis [2] and has since become commonplace in the management of infections in other groups of patients. The Infectious Diseases Society of America (IDSA) published updated recommendations in 2018 regarding patient selection, monitoring, and integration into antimicrobial stewardship [3]. Certain populations such as intravenous drug users and the elderly are recognized as high risk for complications or failure of OPAT [4,5].

Vancomycin is commonly used in OPAT for soft tissue infections and osteomyelitis. The IDSA recommends regularly monitoring vancomycin levels and renal function

during OPAT, though frequency is not specified and this guideline is based on "very low-quality evidence" [3]. Piperacillin-tazobactam (TZP) is often combined with vancomycin when gram negative coverage is necessary; a single-center study of 10,000 patients found this combination twice as likely to cause acute kidney injury (AKI) than either therapy alone [6]. Besides the direct effect on renal function, an additional consideration in using nephrotoxic agents in OPAT is the effect on the serum concentration of medications that depend on renal clearance.

Methotrexate (MTX) is renally-cleared antimetabolite used in the treatment of certain cancers and rheumatological diseases. Side effects include gastrointestinal upset, mucositis, myelosuppression, hepatotoxicity, and, paradoxically, renal impairment [7]. Toxicity is mitigated by giving the lowest effective dose for the indication; high-dose MTX, at least 500 mg/m², is prescribed for oncological use rather than as a disease-modifying antirheumatic drug [8]. We here present a case of severe MTX toxicity occurring in

an elderly patient receiving concomitantly low-dose methotrexate (LDM) for rheumatoid arthritis (RA), and intravenous vancomycin and TZP for osteomyelitis.

2. Case Description

An 86-year-old female with RA, hypertension, diabetes, and osteomyelitis presented from a skilled nursing facility (SNF) with 1 day of painful bleeding from the mouth and gums, hematemesis, and odynophagia. She had no history of facial trauma, recent dental procedures, or bleeding disorders, though she did present to the emergency room 5 days earlier with gingival pain and was discharged without biochemical workup. On arrival, the patient was afebrile with blood pressure 190/87 and heart rate 88. Physical exam was significant for poor dentition, ulcers on the bottom lip, bleeding from the soft palate, a healing, partially resected right 5th metatarsal, and a right upper extremity peripherally inserted central catheter (PICC).

At the SNF the patient was receiving vancomycin 1,250 mg every 12 hours and TZP 2.25 mg every 6 hours through the PICC for osteomyelitis of the right foot, initiated 4 weeks prior during an admission for osteomyelitis. The 4-week TZP course was already completed and there were 2 weeks remaining of the 6-week vancomycin course. Vancomycin trough was therapeutic at 18.6 µg/mL at discharge from the previous admission. Other relevant home medications include weekly oral MTX 12.5 mg and oral prednisone 20 mg daily for rheumatoid arthritis, folic acid, and standing ibuprofen 400 mg as needed for pain.

Laboratory findings were concerning for vancomycin random level of 64.9 µg/mL, blood urea nitrogen 29 mg/dL, creatinine 2.91 mg/dL, glomerular filtration

rate 19 mL/min, white blood cell (WBC) count 2.13 cells/µL, and platelet count 96,000/µL. Patient was admitted for AKI, leukopenia, and thrombocytopenia. Medications were reviewed with the clinical pharmacist in the team. Gingivostomatitis and hematological abnormalities were recognized as consistent with MTX toxicity, so the patient was started on empiric leucovorin 15 mg every 6 hours and folic acid 2 mg daily. Sodium bicarbonate 15 mEq/hr at 100 mL/hr was given to alkalinize urine, thereby facilitating elimination of MTX to a goal of less than 0.05 µmol/L as per Rheumatology consultation recommendation. The first measured MTX level was 0.07 µmol/L on hospital day 4. Low-dose prednisone 5 mg daily was used to provide RA coverage. The patient was started on intravenous fluids to treat the prerenal component of the AKI and help clear renally excreted medications.

On hospital day 2, platelet count dropped to 66,000/µL and WBC count dropped to 1.38 cells/µL. Absolute neutrophil count (ANC) was 96.6 cells/µL, qualifying the patient as severely neutropenic. Per Hematology recommendations, daily filgrastim 300 mcg injections was started with a goal ANC greater than 500 cells/µL. After the patient had a temperature of 100.2°F on day 3, Infectious Disease was consulted and the patient was placed on neutropenic precautions and started on broad-spectrum antibiotics, cefepime 2 gm IV daily and doxycycline 100 mg PO BID for neutropenic fever likely secondary to osteomyelitis. Though serum MTX was at goal by day 6, vancomycin did not drop to a therapeutic level of less than 20 µg/mL until day 8 (Figure 1). Other features of the patient's hospital stay include precipitous decreases in platelet count requiring 1 unit transfusion on day 4 and an ANC that dropped as low as 14.7 cells/µL on day 5, with neutropenia not resolving until day 9.

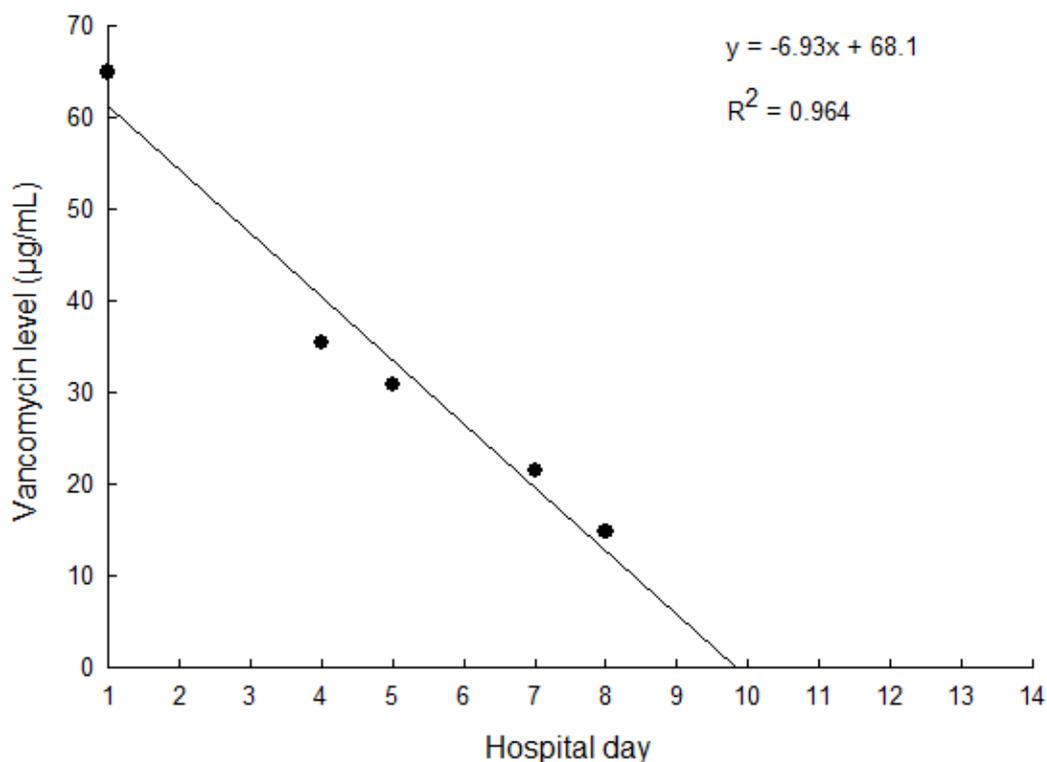


Figure 1. Elimination curve of serum vancomycin

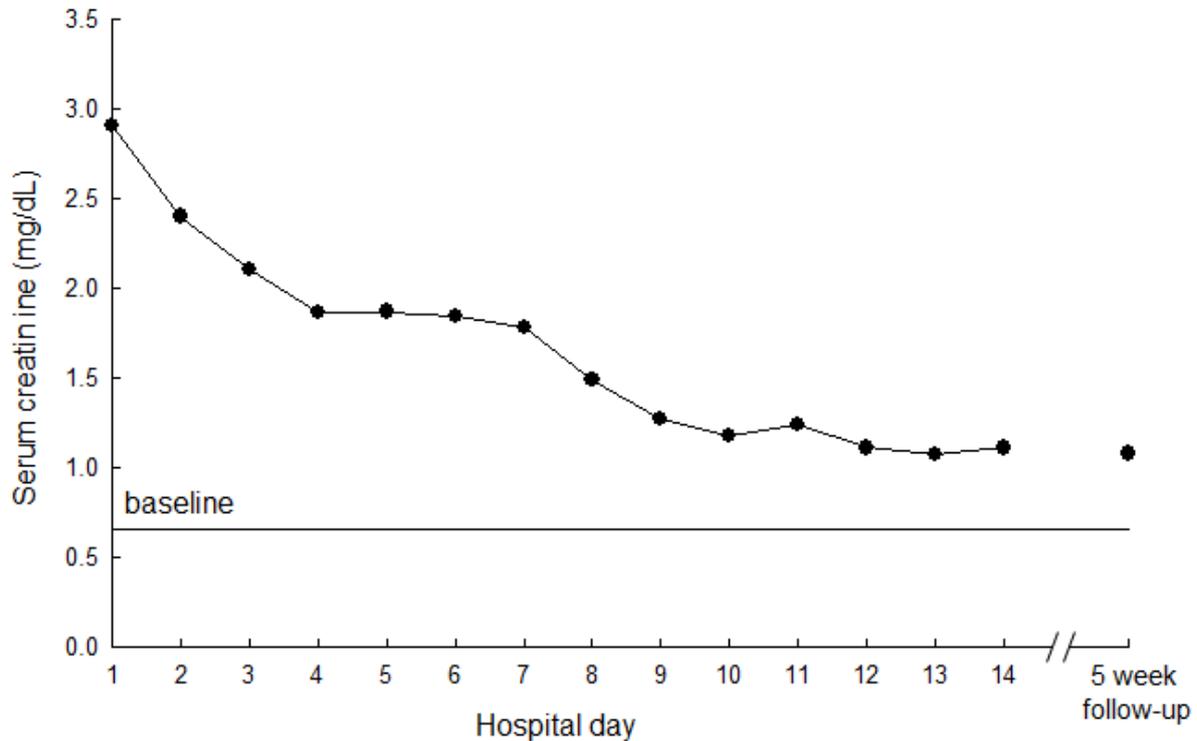


Figure 2. Serum creatinine over time. Horizontal reference line represents baseline 4 weeks prior to admission

The patient was discharged on hospital day 14 after completing a full course of antibiotics and achieving complete resolution of pain symptoms. She was sent out with a simplified medication list including RA monotherapy with prednisone 5mg oral daily and removal of nephrotoxic agents. The AKI improved steadily in response to fluids during the hospital stay, but creatinine did not return to baseline of 0.62 mg/dL, at the 5-week follow-up visit (Figure 2).

3. Discussion

MTX provides its therapeutic effect by competitive inhibition of folate, so folic acid is co-administered to prevent side effects and leucovorin, a biologically active form of folate, is given to reverse acute toxicity [9]. While a systematic review of seven randomized control trials of folic acid co-administration showed statistically significant reduction in hepatotoxicity and gastrointestinal upset, it was underpowered to draw conclusions on preventing nephrotoxicity and myelosuppression [10]. These side effects are more commonly associated with and studied with high-dose MTX used in chemotherapy, though cases of fatal LDM toxicity have been described [11-15]. This patient had been on a stable dose of methotrexate for several years and was receiving appropriate folic acid supplementation, so the sudden appearance of severe MTX toxicity was unusual.

Elderly patients are at high risk of complications from polypharmacy, including adverse drug events and drug-drug interactions [16]. However, impaired renal function was shown to be a stronger predictor of LDM toxicity than age in a pooled analysis of 11 clinical trials with 496 patients [17]. Medication review and confirmation of administration by the SNF raised the suspicion that the

addition of vancomycin and TZP played a role in the patient's AKI, supported by serum vancomycin being three times the upper limit of therapeutic concentration.

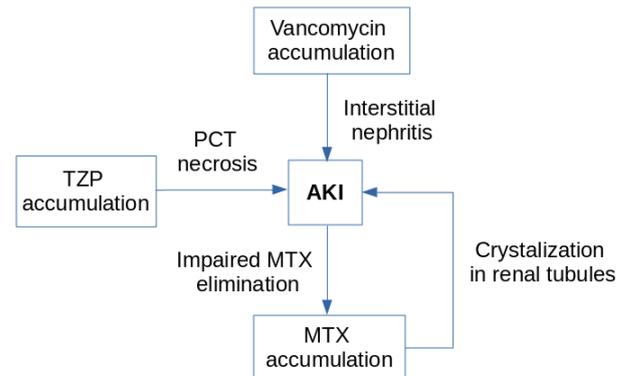


Figure 3. Pathophysiology of acute kidney injury secondary to vancomycin, piperacillin-tazobactam (TZP), and methotrexate (MTX) use. AKI = acute kidney injury, MTX = methotrexate, PCT = proximal convoluted tubule, TZP = piperacillin-tazobactam

Vancomycin causes nephrotoxicity mainly through accumulation in the proximal convoluted tubule, leading to cellular necrosis and glomerular destruction [18]. β -lactam antibiotics, in particular semi-synthetic agents such as piperacillin, are thought to cause AKI through acute interstitial nephritis [19,20]. The increased risk of AKI with the combination of TZP and vancomycin could be caused by these two mechanisms potentiating the effects of one another. The likely series of events was a decrease in renal function caused by vancomycin and TZP, leading to insufficient clearance and intracellular accumulation of MTX. Additionally, MTX itself may lead to nephrotoxicity by crystallization in the renal tubular lumen (Figure 3) [21]. To date, nephrotoxicity from a synergistic effect of LDM, TZP, and vancomycin has not been described.

Worsening pancytopenia in spite of efforts to clear MTX validated early consults to rheumatology and hematology. These services were vital in providing goal levels of ANC and platelet count after filgrastim administration, as well as goal vancomycin and methotrexate levels following cessation of these medications and intravenous hydration with alkaline fluids. Though the patient only had one elevation in temperature, her advanced age, neutropenia, and osteomyelitis led to consultation of the infectious disease service for initiation of broad-spectrum antibiotics. Antibiotic choice for osteomyelitis was within the scope of the primary team, but, given the iatrogenic nature of this patient's presentation a formal, multidisciplinary approach for inpatient management and discharge planning was chosen.

Monitoring renal function and vancomycin levels with routine blood work at the SNF would have likely prevented development of such severe MTX toxicity. Most OPAT research is retrospective and focuses on reasons for treatment failure [22,23]. A recent prospective cohort study of adverse drug events in OPAT showed that female gender and vancomycin use are independent risk factors for having an ADE [24]. This case demonstrates the need for robust surveillance strategies during OPAT in populations at risk for drug toxicities or when using antimicrobials that are regularly measured when administered inpatient.

4. Conclusion

Methotrexate is a renally-cleared antimetabolite used in rheumatoid arthritis and chemotherapy with multi-system toxicities including nephrotoxicity, myelosuppression, hepatotoxicity, mucositis, and gastrointestinal upset. The lower doses used in rheumatologic disease rarely cause severe side effects and have only been described in a small number of case reports. In our elderly patient with no history of kidney disease and several years of low-dose methotrexate use, the addition of vancomycin and piperacillin-tazobactam likely led to acute kidney injury and toxic accumulation of methotrexate, which is also nephrotoxic. Vancomycin and piperacillin-tazobactam may have a synergistic nephrotoxic effect and should be used cautiously in patients taking renally cleared medications with narrow therapeutic indices. This case demonstrates the need for updated guidelines regarding drug choice and biochemical monitoring during OPAT.

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