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Low-dose Methotrexate Toxicity in the Setting of Vancomycin-induced Acute Kidney Injury

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Abstract Methotrexate is a disease-modifying anti rheumatic drug (DMARD) that is often used in low dosages as the first line drug for rheumatoid arthritis patients. The chemotherapeutic agent works by inhibiting dihydrofolate reductase, and the primary route of clearance of the drug is via the kidneys. Kidney injury may delay this clearance and lead to toxic level accumulation of the drug- toxicity presenting as diarrhea, vomiting, mucositis, rash, transaminitis and myelosuppression. Antibiotics such as vancomycin may induce acute kidney injury (AKI) through various mechanisms include damage to the renal tubular epithelial cells. In this report, we describe a case in which an elderly female suffered AKI secondary to vancomycin induced nephrotoxicity. The AKI subsequently led to methotrexate accumulation and toxicity presenting as bleeding mouth ulcers, transaminitis and pancytopenia. The condition was managed with leucovorin rescue therapy and sodium bicarbonate to enhance methotrexate excretion. Renally dosing methotrexate in patients on other nephrotoxic drugs, and monitoring creatinine clearance are methods for preventing such a toxicity.

Keywords: *rheumatoid arthritis, methotrexate, leucovorin, acute kidney injury, pancytopenia, delayed excretion, vancomycin*

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1. Introduction

Methotrexate was first developed as a chemotherapeutic agent for malignancies in the 1940's [1], however, it quickly became a common drug used in lower dosages to manage rheumatoid arthritis. For malignant disease, methotrexate can be used is doses of more than 1g, whereas in rheumatoid arthritis, 7.5 to 25 mg of methotrexate are administered once weekly [2].

The mechanism of action of the drug is to competitively inhibit dihydrofolate reductase, and thus prevent folic acid metabolism [3]. Various steps in amino acid synthesis, and purine and pyrimidine metabolism are dependent on folic acid, and thus these pathways are halted. The drug aims to modulate and suppress inflammation. The primary route of clearance of methotrexate is via the kidneys- about 80-90% is excreted unchanged in the urine, with the remainder undergoing hepatic metabolism prior to renal excretion [4]; therefore, renal function and GFR greatly affect the rate of methotrexate clearance.

Methotrexate toxicity is often seen in patients with reduced methotrexate clearance and increased accumulation due to renal impairment. Toxicity can present as mucositis, stomatitis, pulmonary fibrosis, hepatotoxicity and myelosuppression. The risk of these adverse effects can be reduced by ensuring adequate hydration of patients, and keeping the urinary pH above 7 to reduce methotrexate precipitation within renal tubules and rather promote the drugs excretion [5].

Vancomycin is glycopeptide antibiotic that works by inhibiting cell wall synthesis in gram-positive bacteria. The antibiotic is also mainly eliminated unchanged via renal excretion [6]. The nephrotoxic potential of vancomycin is not well understood, however, the co-administration of vancomycin and piperacillin-tazobactam (Zosyn®) has an odds ratio of acute kidney injury of 3.5 [7]. Therefore, it is recommended that patients receiving vancomycin not be co-administered piperacillin/tazobactam, but instead be given a cephalosporin for gram-negative coverage and metronidazole for anaerobic coverage [8].

The first report of high-dose methotrexate interaction with vancomycin in patients with malignancy was made by Blum et al., which concluded that vancomycin exposure- even without overt renal failure- would delay methotrexate excretion by increasing its toxic effects [9]. They suggested monitoring the patients' glomerular filtration rate while the patient is on vancomycin, so the dosage of methotrexate could be adjusted accordingly.

Here, we report a case of a rheumatoid arthritis patient that suffered methotrexate toxicity due to vancomycin-induced acute kidney injury. The delayed excretion of methotrexate and its subsequent accumulation manifested as toxicity presenting as stomatitis, transaminitis, and myelosuppression.

2. Case Report

An 86-year old woman presented to our institution with right foot pain that had been going on for ten days. Her past medical history was significant for diabetes mellitus, hypertension and rheumatoid arthritis for which she was taking 2.5 mg of oral methotrexate weekly.

The right foot pain was accompanied by swelling, warmth, and peeling skin around the medial malleoli. She also noticed a small "hole" around the base of the 5th digit of her right foot. These findings made it difficult for the patient to ambulate. Other complaints included weight loss and two episodes of vomiting over the last week. No complaint of fever, chills, or cough. MRI was consistent with osteomyelitis, and culture was positive for MSSA. The abscess on the base of the right 5th digit was drained, part of the digit was resected and the patient was started on six weeks of IV vancomycin 1.25 g and IV piperacillin/tazobactam 2.25 g.

Three weeks after discharge- while on the IV vancomycin 1.25 g and IV piperacillin/tazobactam 2.25 g regimen for right foot osteomyelitis- the patient returned to our institution with bleeding from her mouth and gums of one day duration. She complained of mild odynophagia, and one episode of vomiting. There was no trauma to the area, and no bleeding from any other site. Patient had a similar episodes of gum bleeding one week prior. Patient denied headache, fever, chills, and cough.

On physical exam, the patient was afebrile, and hemodynamically stable. She was awake, alert and oriented. She was not in any apparent distress. On examination of her mouth, there were four small 1 mm ulcers on her inner bottom lip and blood surrounding the gums. Her right foot ulcer seemed to be healing well, with no erythema, edema or fluid drainage.

Initial laboratory values were significant for acute kidney injury (Cr 2.9, increased from Cr 0.6 from last visit to our institution), pancytopenia (Hgb 10 WBC 2.1 Platelets 96) and transaminitis (Table 1). At the time of presentation, the patient's measured vancomycin trough level was 65 mcg/mL. For patients with severe infection, such as osteomyelitis, a vancomycin target serum trough level is often in the range of 15 to 20 mcg/mL [10]. At 65 mcg/mL, our patient's trough level was very high, and can be nephrotoxic. The patient's acute kidney injury was most probably secondary to the parenteral IV vancomycin 1.25 g and IV piperacillin/tazobactam 2.25 g antibiotic regimen she was started on three weeks prior for her right foot osteomyelitis. At this time, the patient's antibiotics were held.

The patient's past medical history included a diagnosis of rheumatoid arthritis, which was being managed with five tablets of 2.5 mg oral methotrexate once per week. As mentioned above, methotrexate is excreted renally, and the AKI induced by the antibiotic regimen inhibited adequate clearance of methotrexate. The accumulation of methotrexate resulted in methotrexate toxicity that manifested as oral ulcers, bleeding, pancytopenia due to bone marrow suppression and transaminitis. At this time, the patient's methotrexate was held.

Patient was treated for methotrexate toxicity with leucovorin 12.5 mg oral, and infusion of sodium bicarbonate to increase renal elimination of methotrexate. On discharge (day ten since admission), the patient's methotrexate level was <0.05 umol/L, which is less than the toxic range for this drug. The patients AKI was managed with continuous fluids, and a downwards trend of serum vancomycin levels followed recovery of renal function (at discharge Cr 1.24, at discharge vancomycin level 14.8 mcg/mL, Table 1). The patient's pancytopenia was managed with Filgrastim, a human granulocyte colony-stimulating factor and neutropenic precautions. At discharge, the patient's leukocyte count was 26.51, Hgb was 8.1 and platelets were 101K/uL (Table 1). At this point, the patient was stable and no longer complained of any oral pain or bleeding from her mouth.

For management of the patient's rheumatoid arthritis, the patient was switched from methotrexate to prednisone 5 mg and was discharged to subacute rehabilitation center with a rheumatology follow-up appointment.

Table 1. Laboratory data on initial presentation and discharge

Serum	On presentation	On discharge	Reference
Na	144	141	136-146 (mmol/L)
K	3.4	3.4	3.5-5.5 (mmol/L)
Cl	101	103	98-106(mmol/L)
Glucose	115	100	70-99(mg/dL)
Blood urea nitrogen	29	20	6-20(mg/dL)
Creatinine	2.91	1.24	0.4-12(mg/dL)
Protein total	7.3	6.0	6.0-8.5(g/dL)
Albumin	3.63	2.93	2.8-5.7(g/dL)
Alkaline phosphatase	101	96	25-125(U/L)
AST	98	33	10-35(U/L)
ALT	134	30	0-31(U/L)
Calcium	7.8	7.5	8.4-10.3 (mg/dL)
Magnesium	1.4	1.5	1.9-27(mg/dL)
Phosphorus	3.0	2.0	2.5-5.0(mg/dL)
Total Bilirubin	0.90	0.80	0.0-1.2(mg/dL)
C reactive protein	89.2	89.2	0.0-8.0(mg/L)
ESR	109	109	
Hemoglobin	10.0	8.1	12.0-16.0(g/dL)
WBC	2.1	26.51	4.5-109(cells/mm^3)
Platelets (K/uL)	96.0	101	130-400(K/mm^3)
MTX Level	0.07 (three days after admission)	<0.05	MTX Toxic Range: @ 24 hrs: >10 umol/L @ 48 hrs: >1.0 umol/L
Vancomycin Trough Level	64.9	14.8	15 to 20 mcg/mL

MTX methotrexate.

3. Discussion

Methotrexate is the first line DMARD, and has been widely used in low doses for the treatment of many rheumatological conditions. Over the last two decades, the prevalence of rheumatoid arthritis has increased worldwide. While the safety and efficacy of methotrexate use in the elderly has been demonstrated in many studies, the drug can be severely toxic under certain conditions- such as acute kidney injury.

Low-dose methotrexate toxicity was seen in our elderly rheumatoid arthritis patient, in the setting of acute kidney injury induced by concurrent vancomycin and piperacillin/tazobactam use.

No previous report has been made about low-dose methotrexate toxicity in the setting of vancomycin and piperacillin/tazobactam co-administration. Blum et al. made a report of two patients with osteosarcomas who were receiving high-dose methotrexate as a part of their chemotherapy regimen, and upon vancomycin exposure, it was observed that methotrexate excretion in both patients was delayed and the peak serum level of methotrexate was elevated [9].

In our case and the cases presented by Blum et al., methotrexate accumulation and toxicity secondary to its delayed excretion was induced by vancomycin nephrotoxicity. The effect of vancomycin on nephrons is not well understood. It has been demonstrated in vitro, that vancomycin can change the function of mitochondria and induce proliferation of proximal tubular cells [12]. In animal studies, vancomycin was shown to cause destruction of renal tubular epithelial cells- microscopic examination showed deformed nuclei [13]. In another study of nine patients who suffered vancomycin nephrotoxicity, biopsy of the kidney showed casts composed of vancomycin aggregates in the renal tubules [14]. Therefore, from these studies it can be concluded that vancomycin nephrotoxicity damages the renal tubules- a major site of methotrexate excretion. The delayed excretion of methotrexate due to damaged renal tubules leads to the drugs eventual accumulation, prolonged exposure and toxicity.

Many guidelines have been suggested for adjusting methotrexate dosage based on renal function and degree of impairment. Measurement of serum creatinine as an evaluation of renal failure was suggested to be not enough in the 2004 Methotrexate and Renal Insufficiency study. Instead the study proposed measurement of creatinine clearance [15]. The University College Long Hospital suggested reducing the methotrexate dose to 65% for creatinine clearance below 60 ml/min and to 50% for creatinine clearance below 45 ml/min, and to hold vancomycin the if creatinine clearance was under 30 ml/min [16]. Guidelines per The American College of Rheumatology indicate routine blood tests, complete blood count, liver function test, and creatinine every 12 weeks if the patient has been on methotrexate for more than six months [17].

Once methotrexate toxicity has been diagnosed, the goal becomes to enhance its excretion. This can be done by giving folinic acid to replenish stores of folic acid so, the uptake of methotrexate can be inhibited. Hydration with >3 L/m2 per day to maximize urine output can also enhance methotrexate excretion [18]. Alkalization of the urine with oral sodium bicarbonate which enhances methotrexate excretion by increasing methotrexate solubility while preventing the formation of methotrexate crystals that form in acidic urine. These were the three methods used in our patient. This triple approach was maintained until a target methotrexate level of less than 0.05–0.1 mM was reached [19]. Other methods of elimination include dialysis and plasma exchange.

4. Conclusion

Methotrexate is the first line DMARD used in low-doses for rheumatoid arthritis due to its efficacy and safety in the elderly. However, the dose of methotrexate must be renally adjusted in patients taking nephrotoxic drugs or who have underlying renal injury. Renal dose adjustment was overlooked in our patient, who suffered acute kidney injury induced by vancomycin use and eventual methotrexate toxicity. Monitoring patients' creatinine clearance is one way of assessing their renal function. These steps are critical for preventing methotrexate toxicity, which can present as pancytopenia, stomatitis, and transaminitis- all signs seen in our patient. Management includes intense hydration, alkalization of the urine and replenishment of intracellular folic acid stores.

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