

## Low Dose Methotrexate Toxicity Leading to Death in the Intensive Care Unit

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### Introduction

Methotrexate toxicity has been widely shown to cause myelosuppression but the literature demonstrating low doses of the drug causing the same issue is much scarcer. Our patient presented with severe pancytopenia which began to improve with treatment but she ultimately succumbed to a superimposed pneumonia.

### Case

Our patient is a 65-year-old female with a past medical history significant for rheumatoid arthritis (RA) who presented to the emergency department with a chief complaint of bleeding oral ulcers. The ulcers had been present for 3 weeks before the patient presented but she started developing malaise and had subjective fevers at home so she came to the emergency department. RA had been well controlled on low dose 7.5 mg methotrexate weekly with folic acid supplementation for five years. Physical exam was significant for an ill appearing female with swollen and bleeding lips with no joint deformities were seen. Initial lab work was significant for severe pancytopenia with white blood cell count (WBC) of 0.4 K/UL with a calculated absolute neutrophil count of 0 cells/uL, hemoglobin (Hb) of 8.6 g/dL, and a manual platelet count of 42 K/UL. Patient also had acute kidney injury with blood urea nitrogen (BUN) of 48 mg/dL, creatinine (Cr) of 1.20 mg/dL, and a Cr clearance of 20 ml/min. The Intensive care unit (ICU) was consulted for severe pancytopenia. A methotrexate level was sent. Patient spiked a fever of 102.5F and soon became hypotensive to 85/65 mmhg. A Code Sepsis was called and patient was aggressively resuscitated with 30cc/kg of normal saline; blood, sputum, urine cultures were sent, and broad spectrum antibiotics were started along with Leucovorin and folic acid. Methotrexate levels came back at 0.5 mcmol/L. On ICU day three her WBC count improved to 4.2 K/UL and her renal function improved. All initial cultures came back with no growth. On day five of admission she became acutely short of breath and was found to be de-saturating to 70% on room air. CT angiography was ordered to rule out pulmonary embolism which revealed new bilateral airway opacities with lower lobe consolidation and upper lobe opacities with ground glass attenuation concerning for multifocal pneumonia. She was intubated due to hypoxic respiratory failure and septic bundle was re-started. Repeat cultures were sent that showed heavy growth of MRSA in the sputum. Her clinical status deteriorated and multi-organ failure ensued. She became acidotic despite full resuscitation and expired on day seven of her hospital stay.

### Discussion

There is not much literature showing rapidly fatal cases of low dose methotrexate toxicity causing pancytopenia. Methotrexate is a first line disease-modifying anti-rheumatic drug (DMARD) in the treatment of RA with a favorable side effect profile. Methotrexate toxicity is generally seen at high doses normally used in malignancy. However, our patient was on the lowest dose used in RA which ranges from 7.5 to 25 mg weekly. The Matrix study (Methotrexate and Renal Insufficiency study) was conducted in 2004 and suggested following creatinine clearance measurement as opposed to creatinine while dosing methotrexate [1]. Preventative measures include holding medications that can lead to increased toxicity by leading to decreased renal elimination. (Aminoglycosides, cyclosporine, sulfa drugs, salicylates, cisplatin, and colchicine) [2].

The American College of Rheumatology advise that methotrexate levels should be monitored every 2-4 weeks for the first 3 months, every 8-12 weeks for the next 3-6 months and every 12 weeks for those on the drug for more than 6 months. Laboratory tests that should be monitored are complete blood count (CBC), liver function testing and creatinine [3]. According to the University College London Hospital methotrexate is well absorbed at doses < 30mg/m<sup>2</sup> with bioavailability decreased by food and milk. Metabolism is via liver and intracellular metabolism to polyglutamated products. The drug is excreted primarily by the kidneys (90%) although small amounts are secreted via the bile. Clearance is higher in children than in adults. Their recommendations are to give 100% dosing for CrCl (ml/min) over 80, 65% of dose for CrCl 60, 50% of dose for CrCl 45 and then to hold methotrexate completely for CrCl <30. Although these are not standard of care guidelines if these had been followed our patient would not have been on methotrexate as her CrCl was 20 [4].

In a review by Shaye, et al. clinical characteristics and risk factors for low dose methotrexate toxicity looked at a cohort of 28 patients. Pancytopenia was the most frequent manifestation of toxicity. Risk factors included acute renal failure hypoalbuminemia, proton pump inhibitors, and non steroidal inflammatory medications. Drug level monitoring did *not* correlate with the degree of pancytopenia. In this study 25% of patients with methotrexate toxicity died from pancytopenia related-sepsis [5]. This suggests there is no rationale for methotrexate therapeutic drug monitoring in low dose toxicity. In our patient her drug level was normal to low and did not correlate

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the severity of her presentation. This suggests again that her creatinine clearance was likely the reason methotrexate toxicity and pancytopenia ensued.

### Conclusion

Pancytopenia can occur even with low dose methotrexate. It is important to monitor labs at least every 12 weeks. A review of the literature suggests that creatinine clearance is a much better tool for determining dose than creatinine and glomerular filtration rate. Even if the methotrexate level is low in the blood it is reasonable to consider holding methotrexate in patients with a creatinine clearance less than 30.

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