Methotrexate toxicity: The Systemic Impact on the Human Body

Asad Mussarat, MD; Luke Yesbeck, DO; Angus Harper, MD; Ahmed Fazal-ur-rehman, Rebecca Maitski, Seth Vignes, MD; Brian Mackel, MD

Case study: Patient is a 74-year-old female with a past medical history of psoriatic arthritis, recent right above knee amputation, and recurrent UTIs who presented with chief complaint of urinary incontinence and generalized weakness for 5 months. She had multiple UTIs within the 5-month period treated with cephalexin. For the past month, she began having watery diarrhea with both bright red blood and melena in her stools, nausea, and vomiting. She later developed dysphagia and odynophagia one week prior to admission. She also reported bleeding from her gums, and slowly healing abrasions on her upper extremities from a fall one week prior. Patient's medications include methotrexate, and hydroxychloroquine for seven years. Non-scrapable leukoplakia was present on the surface of her tongue, and mucosal injuries were appreciated on the upper and lower lip. The left lower extremity was warm and erythematous while her right lower extremity amputation site showed purulent, poorly healing wounds. Vitals were stable. Complete blood count was pertinent for WBC of 0.7 x 10^3/uL, hemoglobin 8.8 gm/dL, hematocrit 26.9%, and a platelet 21x10^3/uL. AST and ALT were mildly elevated with 41 U/L and 50 U/L, respectively. The ferritin level was 955 ng/mL (reference 7.3-270.7) and C-reactive protein was 19.1 mg/dL. The reticulocyte count was 0.59 %, and folic acid levels were 2.9 ng/mL (>5.4 ng/mL). Methotrexate (MTX) levels were <.20 µmol/L (reference <0.01 µmol/L). No splenomegaly was appreciated on CT abdomen or pelvis. Urine cultures were concerning for *E. Coli.* Superficial wound cultures from amputation stump were positive for *Streptococcus agalactiae.* With concerns for methotrexate toxicity, methotrexate and hydroxychloroquine were held and patient was started on a 7-day course of Leucovorin therapy and broad-spectrum antibiotics. The patient's labs significantly improved closer to baseline within onw week and her mucositis and wounds started to heal appropriately. Patient was discharged to skilled nursing facility on hydroxychloroquine; methotrexate was discontinued, and patient was referred to a a rheumatologist to follow up with

Discussion: Methotrexate toxicity encompasses a broad spectrum of adverse effects ranging from gastrointestinal symptoms to life-threatening complications such as myelosuppression. The incidence of MTX toxicity varies depending on factors such as pharmakinetics, concomitant medications, and individual patient characteristics. The pathophysiology of MTX toxicity involves interference with folate metabolism, leading to impaired DNA synthesis and cell proliferation. Folate supplementation mitigates these effects by providing a substrate for essential cellular processes, thereby reducing the risk of adverse events. Close monitoring of serum MTX levels and renal function guides treatment decisions, with consideration given to dose adjustment or drug discontinuation in severe cases.

Conclusion: Methotrexate toxicity is a potentially life-threatening complication of MTX therapy that requires prompt recognition and intervention. Clinicians should be vigilant for signs and symptoms of toxicity, particularly in patients with risk factors predisposing to adverse drug regarding the importance of folate supplementation and regular follow-up is essential for optimizing therapeutic outcomes and minimizing the risk of MTX toxicity.