Case Report: A Case of Methotrexate Intoxication Presenting as a Pseudo-Disseminated Herpes Zoster Infection

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Case Presentation:
A 55-year-old woman consulted to the emergency department with a chief complaint of abdominal pain and skin lesions. She was transferred to our institution with a diagnosis of acalculous cholecystitis along with a pancytopenia of unknown etiology.

The patient had a personal history of Crohn's disease treated with adalimumab and methotrexate (MTX), the latter of which had been prescribed orally 15 mg once per week. She was also known for a mixed anxiety-depressive disorder.

Upon arrival, the patient was transferred to the intensive care unit (ICU) and rapidly intubated secondary to agitation and to facilitate central venous access for her transfusion needs. On examination, she presented stomatitis along with multiple superficial skin ulceration on her extremities (Figure 1). Upon questioning the patient's medication, she couldn't tell us precisely her MTX intake and confirmed that she had been confused regarding the correct posology. With her consent, we got access to her pill container. Her last refill dated from two weeks earlier, with a total of seventy-two pills prescribed. With the help of the pharmacist, we concluded that there should have been sixty pills remaining with a significant MTX overdose.

On admission, investigations revealed a pancytopenia. (Hemoglobin 66 g/L, white blood cell count 1.6 × 109/L and platelet 12 × 109/L). She had an elevated C-reactive protein (180 mg/L) and sedimentation rate (83 mm/h). Her metabolic panel showed an alkaline phosphatase of 220 UI/L, ALT of 100 UI/L, AST of 80 UI/L, albumin of 26 g/L, INR 1.0 and creatinine 50 µmol/L. An extensive panel, including ANCA, cryoglobulin, complements, hepatitis serology, blood cultures and HSV-PCR tests were all negative. Her MTX and adalimumab had been stopped five days before admission. The patient was put on piperacillin-tazobactam and intravenous acyclovir and had a percutaneous cholecystostomy performed. After a short ICU stay, the patient was transferred to the general ward.

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The patient improved and was discharged a week later. She had a follow-up appointment with her gastroenterologist who discontinued her MTX medication. A psychiatry consultation revealed an unspecified cluster B personality disorder and it was concluded that her condition had contributed to the incorrect pill intake. A bubble pack was prescribed and counseling was offered to the patient to reduce the risks of subsequent intoxication.

Keywords: Intoxication; Anxiety-depressive disorder; Patient's medication; Acute cholecystitis
Discussion

Methotrexate is an analog of folic acid and inhibits dihydrofolate reductase and thus the synthesis of folic acid. Folic acid is essential for DNA synthesis and repair. It is used in the treatment of autoimmune inflammatory and neoplastic diseases, such as rheumatoid arthritis and psoriasis [1]. As seen in this case, MTX can be associated with multiple potential adverse effects, most commonly involving the gastrointestinal tract. Mucositis is caused by the suppressive effect of MTX on cell proliferation. At higher doses, bone marrow suppression is seen [1]. Also, our patient presented with hypalbuminemia, which has been known to increase the clearance time of high doses of methotrexate [2]. Our patient presented with severe pancytopenia which might have contributed to an increased risk of developing infections, such as an acute cholecystitis and disseminated herpes zoster, although the latter was less probable considering three negative herpes simplex virus (HSV) polymerase chain reaction (PCR) skin testing and atypical skin lesions.

Skin lesions due to acute MTX toxicity are rare and can include reactions such as ulcer, erythema multiforme, toxic epidermal necrosis, Stevens-Johnson syndrome, exfoliative dermatitis or skin necrosis [3,4]. Our patient presented with ulcerated skin lesions that could have been caused by drug toxicity. Furthermore, the recognition of a possible concomitant intoxication took several days for multiple reasons. First, the patient had been intubated on admission, which prevented us from obtaining a clear history. Second, the patient had multiple confounding factors, including an acute cholecystitis which could have explained the pancytopenia. Third, the patient presented multiple episodes of confusion and disorientation that made the evaluation of a possible intoxication difficult. Seeing as a concomitant herpes simplex infection was improbable, we agreed that the clinical picture was compatible with methotrexate intoxication. It came clear that our patient had a misunderstanding of the correct posology of the medication. An Australian database identified twenty-two deaths linked with MTX, including seven cases in which erroneous daily dosing was documented. Reasons for the errors included patient misunderstanding and incorrect packaging of dosette packs by pharmacists [5]. Too often, MTX intended for once weekly administration is inadvertently and tragically taken daily [6]. The toxic effects of methotrexate on normal tissues are more of a function of the duration of exposure to suprathreshold concentrations of the drug rather than peak levels achieved [7]. A 2004 publication of all MTX adverse-event reports submitted to FDA between 1997-2001 reported 25 deaths related to medication errors. The most common types of errors involved confusion about the once-weekly dosage schedule (30%). Of the errors, 37% were attributable to the prescriber, 20% to the patient, 19% to dispensing, and 17% to administration by a healthcare professional [8].

For more than 30 years, folic acid rescue has been a cornerstone of methotrexate toxicity, which is applied in a variety of adult and pediatric cancers, including acute lymphoblastic lymphoma, osteosarcoma, and lymphomas. It is particularly effective in the prevention of myelosuppression, gastrointestinal toxicity, and neurotoxicity in patients having received high doses methotrexate such as 500 mg/m², which are values significantly higher than our patient’s case [9].

Conclusion

In our case, the serum methotrexate level was negative. However, the drug’s half-life would have allowed complete renal clearance of the drug in the two weeks’ interval since the last intake. At that time, there was no benefit of adding folic acid considering the time lapse since the last dose and the clinical improvement of the patient.

Our case presented a 55-year-old woman, with multiple psychiatric comorbidities, who presented with a combination of pancytopenia, mucositis and ulcerated skin lesions secondary to inadvertent methotrexate intoxication. This case illustrates the importance of early recognition in the face of a potential medication intoxication, which led to the interruption of methotrexate. Healthcare providers need to be informed about the potentially devastating consequences of a dosage error to their patient. Face-to-face counseling and supplemental written information should be provided, especially to vulnerable patients, such as older adult, patients with comorbid psychiatric conditions and patients with chronic kidney diseases. A system which would limit the number of accessible drugs to any given patient should be implemented. In the meantime, a physician that witnesses a situation that would put a patient at risk of an adverse event should rapidly intervene.

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References