

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

Mathieu Boudreau-Frenette^{1*}, Gabriel Girouard², Centre de Formation Medicale du Nouveau-Brunswick³

¹Department of Medicine, Universite de Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, Quebec, J1H 5N4 Canada

²Division of Medical Microbiology and Infectious Diseases, Dr. Georges-L.-Dumont University Hospital Centre,

330 University Avenue, Moncton, New Brunswick, E1C 2Z3 Canada

³Centre de Formation Medicale du Nouveau-Brunswick 100 Aboiteaux Street, Moncton, New Brunswick, E1A 7R1, Canada

*Corresponding author: Mathieu Boudreau-Frenette, Department of Medicine, Universite de Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, Quebec, J1H 5N4 Canada, E-mail: mathieu.boudreau-frenette@usherbrooke.ca

Received date: September 30, 2018; Accepted date: October 15, 2018; Published date: October 20, 2018

Copyright: © 2019 Frenette MB, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background

Oral Methotrexate (MTX) intoxication is an uncommon, but potentially fatal situation.

Case presentation

We report the case of a 55-year-old woman who suffered from an inadvertent MTX intoxication caused by erroneous daily ingestion. She presented with recurrent bouts of febrile pancytopenia with associated skin lesions suspected initially to be a disseminated herpes zoster infection. Multiple negative Herpes Simplex (HSV) and Varicella-Zoster Virus (VZV) PCR testing along with a confirmed medication misuse established our diagnosis.

Conclusion

This case illustrates the importance of early recognition of MTX toxicity, which can have potentially devastating consequences. Healthcare providers need to be informed about the diverse clinical presentations of MTX intoxication and maintain a high degree of clinical suspicion with any patients exposed to this drug.

Keywords: Methotrexate toxicity; Disseminated herpes zoster; Medication misuse; Stomatitis; Pancytopenia

Case Presentation

A 55-year-old woman consulted in another hospital with a chief complaint of abdominal pain and skin lesions. After two days, she was transferred to our tertiary care center with a diagnosis of recurrent bouts of febrile pancytopenia, an acalculous cholecystitis, and a clinical suspicion of disseminated herpes zoster necessitating airborne precautions.

The patient had a personal history of Crohn's disease treated with adalimumab and Methotrexate (MTX), the latter of which was prescribed 15 mg weekly oral dose along with folic acid 15 mg. Six months earlier, she was hospitalized with a similar presentation (febrile pancytopenia with stomatitis). She was also known for a mixed anxiety-depressive disorder.

Upon her arrival to our center, the patient was transferred to the Intensive Care Unit (ICU) and rapidly intubated in the context of agitation and to facilitate central venous access for her transfusion needs. Upon examination, it was found that she had extensive stomatitis along with multiple skin ulcerations on her extremities (Figure 1).



Figure 1: Superficial ulcerated skin lesion (left lesion) on ankle.

Investigations revealed a pancytopenia (hemoglobin 66 g/L, white blood cell count $1.6 \times 10^9/L$ and platelet $12 \times 10^9/L$). She had an elevated C-reactive protein (180 mg/L). Her metabolic panel showed an alkaline phosphatase of 220 UI/L, ALT of 100 UI/L, AST of 80 UI/L, and albumin of 26 g/L, INR of 1.0 and creatinine of 50 $\mu\text{mol/L}$. An extensive panel, including anti-nuclear antibody, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, porphyrin urine screen, cryoglobulins, complements, viral hepatitis, HIV and syphilis serology,

blood cultures and skin HSV/VZV PCR tests, were all negative. Her MTX and adalimumab had been stopped before her transfer to our hospital. The patient was put on piperacillin-tazobactam, intravenous acyclovir and had a percutaneous cholecystostomy tube inserted. She received blood and platelet transfusions. A skin biopsy was also performed. After a short ICU stay, the patient was transferred to the general ward for convalescence.

Upon questioning, the patient 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 MTX bottle. Her last refill dated from two weeks earlier, with a total of seventy-two pills prescribed (2.5 mg each). We concluded that there should have been sixty pills remaining with a respected posology of six pills weekly. However, there were only thirty pills remaining in the container, thus confirming a significant MTX overdose. We performed a serum MTX dosage two weeks after her last presumed intake which came negative. The patient didn't receive leucovorin rescue therapy.

The pancytopenia corrected progressively with normalization of the blood count after two weeks. A skin biopsy demonstrated intra-epidermal vesicles with keratinocytes that displayed ballooning degeneration and acantholysis. Some of the keratinocytes were multinucleated and contained pale ground-glass inclusions resembling a herpetic infection. We attributed her acute acalculous cholecystitis to MTX mucosal and digestive tract toxicity [1].

The patient was discharged after two weeks of hospitalization. She had a follow-up appointment with her gastroenterologist who discontinued her MTX. A psychiatric consultation revealed an unspecified cluster B personality disorder, and it was concluded that this condition had contributed to the incorrect pill intake. A bubble pack was prescribed for her other drugs and counseling was offered to the patient to reduce the risks of a subsequent intoxication.

Discussion

MTX is an analog of folate and inhibits dihydrofolate reductase, and thus the synthesis of folic acid. Folic acid is essential for DNA synthesis. MTX is used in the treatment of oncological and non-oncological diseases, such as rheumatoid arthritis, psoriasis and certain forms of leukemia, to name but a few. MTX can be associated with multiple potential adverse effects, most commonly involving the gastrointestinal tract. At higher doses, bone marrow suppression is seen [2]. Mucositis and skin erosions are caused by keratinocyte dystrophy and subsequent skin fragility [3]. Skin lesions due to acute MTX toxicity are still rare and can include ulcers, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis [4]. A retrospective case series study described common histologic skin features of five consecutive patients, which included focal necrosis of keratinocytes within the epidermis, severe keratinocyte dystrophy and multinucleate keratinocytes [5]. Our patient had mouth and skin ulcers that were finally attributed to MTX toxicity. Mouth lesions and two skin ulcers swabs were negative for HSV and VZV by PCR tests.

The recognition of a possible MTX intoxication took several days for multiple reasons. First, the relapsing character of her condition was not grasped immediately upon transfer. Secondly, the patient had been intubated on admission, which prevented us from obtaining a clear history. Finally, the patient had multiple confounding factors, including an acalculous cholecystitis and febrile neutropenia. It became clear that our patient had a misunderstanding of the correct

posology of her medication. An Australian database identified twenty-two deaths linked to MTX intoxication, 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 [6]. A 2004 publication of all MTX adverse-event reports submitted to the FDA between 1997-2001 reported 25 deaths related to medication errors. The most common types of errors involved confusion regarding the once-weekly dosage schedule (30%). Of those errors, 37% were attributable to the prescriber, 20% to the patient, 19% to dispensing, 17% to administration by a healthcare professional and 7% unspecified [7]. Too often, MTX intended for once-weekly administration is inadvertently taken daily [8]. The toxic effects of MTX are generally related to the duration of an exposure above a suprathreshold concentration rather than a single peak level [9].

For more than 30 years, folic acid has been a cornerstone approach to reduce MTX toxicity. On the other hand, folinic acid (leucovorin) is used as a MTX antidote in case of impaired excretion of the drug or overdoses.

In our case the serum MTX level was negative. That said, the drug's half-life (three to ten hours) would have allowed its complete renal clearance in the two weeks' interval since the last intake. At that time, there was no benefit of adding folinic acid, especially considering the clinical improvement of the patient.

This case illustrates the importance of recognizing potentially highly toxic medications in a patient's drug chart. Surprisingly, despite the patient presenting a similar clinical spectrum six months prior, no one had initially suspected MTX intoxication as a potential culprit. This finding led to the interruption of the MTX treatment and to the prevention of further harm. Healthcare providers need to be informed about the potentially devastating consequences of a dosage error with MTX. Face-to-face counseling and supplemental written information should be provided, especially to vulnerable patients such as the elderly, patients with psychiatric conditions, and patients with chronic kidney diseases.

Funding

This research was supported in part by a grant from the Centre de formation médicale du Nouveau-Brunswick.

References

1. Caihong Q, Ying L, Weimin L (2017) Severe Bone Marrow Suppression Accompanying Pulmonary Infection and Hemorrhage of the Digestive Tract Associated with Leflunomide and Low-dose Methotrexate Combination Therapy. *J Pharmacol Pharmacother* 8 : 35-37.
2. Knoll K, Anzengruber F, Cozzio A, French LE, Murer C, et al. (2016) Mucocutaneous Ulcerations and Pancytopenia due to Methotrexate Overdose. *Case Rep Dermatol* 8: 287-293.
3. Delyon J, Ortonne N, Sbidian E, Chosidow O (2016) Keratinocyte Dystrophy as a Marker of Low - Dose Methotrexate-Induced Skin Toxicity: Comment on the Clinical Image by Monch et al. *J Arthritis Rheumatol* 68 : 1790-1791.
4. Tekur VK (2016) Methotrexate-induced nonhealing cutaneous ulcers in a nonpsoriatic patient without pancytopenia. *Indian Dermatology Online Journal* 7 : 418-420.
5. Delyon J, Ortonne N, Benayoun E, Moroch J, Wolkenstein P, et al. (2015) Low-dose methotrexate-induced skin toxicity: Keratinocyte dystrophy as a histologic marker. *J Am Acad Dermatol* 73: 484-490.

6. Cairns R, A Brown J, Lynch AM, Robinson J, Wylie C, et al. (2016) A decade of Australian methotrexate dosing errors. *Med J Aust* 204 : 384.
7. Moore TJ, Walsh CS, Cohen MR (2004) Reported medication errors associated with methotrexate. *Am J Health Syst Pharm* 61: 1380-1384.
8. Simonson W (2015) Daily methotrexate can be lethal! *Geriatric Nursing* 36: 224-225.
9. Lim AY, Gaffney K, Scott DG (2005) Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. *Rheumatology* 44: 1051-1055.