www.mednet.gr/archives
ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Oral complications due to methotrexate use by an old woman

Severe oral ulcerations may occur as an adverse effect caused by the use of methotrexate. The case of a patient is reported in whom the hypothesis of this complication was not raised before hospitalization which favored the diagnosis and control of the injuries in a short time. The patient was in irregular use of methotrexate and suffered concomitant traumatic facial injuries due to a recent accidental fall, contributing to the initial diagnostic challenges. Recurrent oral ulcerations had been present some months before and healed spontaneously, while admission lesions were also due to dental elements erosions damaging soft tissues. She underwent associated low-level laser and antimicrobial photodynamic therapies, which have been a cornerstone option to get analgesia, accelerated repair, and early oral feeding. As oral ulcers may occur during methotrexate utilization, more attention is needed to seek for specialized evaluation about the drug induced adverse effects and respective treatments.

ARCHIVES OF HELLENIC MEDICINE 2025, 42(2):271–273
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2025, 42(2):271–273

L.C. Bittencourt,[1]
V.M. dos Santos[2]

[1]Specialist in Hospital Dentistry, Brasília-DF
[2]Armed Forces Hospital and Catholic University of Brasília-DF, Brasília-DF, Brazil

Στοματικές επιπλοκές λόγω χρήσης μεθοτρεξάτης από ηλικιωμένη γυναίκα

Περίληψη στο τέλος του άρθρου

Key words

Drug adverse effect
Low-level laser therapy
Methotrexate
Oral ulcer

Submitted 3.2.2024
Accepted 16.3.2024

Oral lesions developed by adverse effects of methotrexate (MTX) can be managed by the use of low-level laser therapy (LLLT) and antimicrobial photodynamic therapy (aPDT).[1–8] MTX is a folic acid antagonist by inhibiting the conversion of dihydro- to tetrahydrofolate, affecting the proliferation of high-turnover cells as medullary and oral epithelial cells; the development of pancytopenia represents the major overwhelming risk of this effect.[1,5,6] Treatment with MTX may cause oral lesions and other disorders by overdose toxicity, or cumulative levels of the drug in patients who present with deficit of the renal function.[1,3,5,6] Interestingly, stomatitis is a frequent adverse effect of MTX in the treatment of malignancy, but is uncommon in patients using this medication to treat rheumatoid arthritis (RA).[6] The adverse effects are more often of low and moderate intensity, and the most common manifestations are oral, gastrointestinal, neurological, rash, alopecia, and anaphylaxis.[1,3,5,6] While the more severe are bone marrow and lung toxicity, liver fibrosis and cirrhosis, pancytopenia or immunosuppression are the ominous effects which can be rapidly fatal.[1,3,5,6] As the complications generated in the oral cavity constitute a very favorable environment for the development of infections, the approach is the same for the curative management. The first choice is LLLT utilizing less than 100–200 mW, that are associated with an effective anti-inflammatory action accelerates tissue repair, reducing edema and pain; methylene blue is used with topical applicator associated with light for disinfection.[2,4,7,8]

The aim of this report is enhancing the suspicion index of health care workers about the drug induced oral manifestations to get the early diagnosis and a prompt due management.

CASE PRESENTATION

A 72-year-old Brazilian woman with RA, in use of losartan, metformin, and MTX at low doses (up to 25 mg/week), was admitted due to a fall from her own height and complaining of painful lesions in the mouth. One year ago, an imaging study of the head was performed revealing sequels of ischemic injuries in the periventricular and subcapsular regions of the brain, related to the instability of the gait; there was also a visual difficulty to control her medications. She had a shallow ulcerated lesion on the lower lip, and lower teeth with chronic erosions, besides bleeding facial lesions caused by trauma resulting from the fall (fig. 1A). Laboratory tests showed hemoglobin 9.5 g/dL, hematocrit 27.5%,

platelets 78,000/mm^3, leukocytes 300/mm^3, and urea 63 mg/dL recognized factors predisposing to hemorrhages, infections, and drug adverse effects. She underwent a total blood transfusion, one unit of whole blood derived platelets per 10 kg of weight, besides the folinic acid (50 mg 6/6 hours IV) and filgrastim (300 µg daily IV), while the blood level of MTX was less than 0.20 µmoL/L. The large-spectrum antibacterial prophylactic schedule for sepsis, associated with fluconazole was immediately administered because of the accentuated neutropenia. The lesions were successfully cured through four sessions of 4 Joules LLLT plus aPDT, which provided rapid and progressive improvement of pain and edema, in addition to the *restitutio ad integrum* of tissue structures in affected areas of the face, as well as the mouth. Figure 1B–1C shows the resolutive steps of the local employed management. While the schedule of MTX was also adequately adjusted, the patient family had detailed information about possible manifestations of eventual adverse effects of this medication. Her follow-up has been unremarkable, without development of other oral manifestations. This patient presented the classic clinical evolution of a chronic MTX intoxication, with mucositis and thrombocytopenia, controlled with dose adjustment and a dentistry treatment.

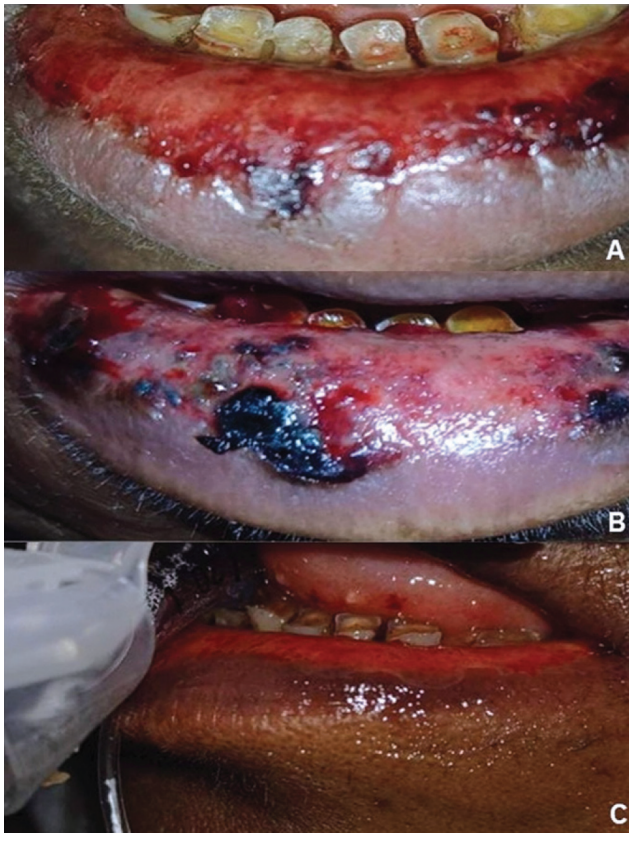

Figure 1. Gross views of the favorable evolutive aspects presented by the oral lesions after four sessions of local low potency laser therapy plus antimicrobial photodynamic therapy. Notice the inferior dental elements with erosions that easily can cause soft tissue lesions.

DISCUSSION

MTX inhibits cell proliferation with major consequences in cells with high turnover and reduced half-life; therefore, when the oral epithelium is affected occurs mucositis which can be associated with bleeding by thrombocytopenia, and infections due to cytopenia.[1,3,5,6] The manifestations may be acute (in less than seven days of use) or chronic, being more often caused by high doses, but the more frequent toxicity follows an accidental overdose.[1,3,5,6] High doses may be due to a logistical error or the patient accidentally taking too much drug.[5] Data of oral ulcers caused by low-dose MTX are limited to single cases or series of cases;[3] the blood levels potentially toxic of MTX depend on the period after the last drug ingestion, ranging from over 10.00 µmoL/L in 24 hours, and 1.00 µmoL/L in 48 hours, or 0.20 µmoL/L in 72 hours. It is worthy of note that these painful ulcers without antecedent of trauma and resistant to usual management are not usually diagnosed by health professionals as a side effect of MTX; another concern is the lack of consensual protocol to guide the treatment of these ulcers.[3] The decision between the options for managing oral ulcers may have different approaches. In the present case study, the laser therapy was preferred to treat traumatic injuries as the first option considering the possibility of necrosis occurrence in case of suturing, because the wound was superficial and presented an active bleeding resultant of thrombocytopenia. The results of the LLLT depend on the local, besides the individual patient conditions.[2,4,7,8] The utilization of LLLT in periodontal, peri-implant and other conditions increased due to the role on the inflammation control, healing acceleration, and reduction of the morbidity.[4] Furthermore, the photobiomodulation by LLLT can reduce the inflammatory phenomena of the traumatic ulcers in experimental animals, by stimulating the fibroblasts production and an enhanced production of collagen, to heal the ulcers, including in a diabetic animal.[2]

In conclusion, the use of MTX can cause oral ulcers and specialist assistance is important at the initial symptoms, because in cases needing hospitalization the mucosa may already present complications and bleeding. In the present report, the treatment utilizing LLLT plus aPDT in addition to the correct administration of MTX resulted in success, without recurrence. The authors believe that even single case reports enhance the awareness about occurrences of unsuspected moderate to severe adverse side-effects of longstanding use of medications. Moreover, the role of dentistry specialists in multidisciplinary teams should be highlighted.

Author contributions

The authors confirm their contribution to the paper as follows: Study conception and design: Bittencourt LC and dos Santos VM; data collection: Bittencourt LC and dos Santos VM; analysis and interpretation of results: Bittencourt LC and dos Santos VM; draft manuscript preparation: Bittencourt LC and dos Santos VM. All authors reviewed the results and approved the final version of the manuscript. All authors agreed to be responsible for all aspects of the work to ensure the accuracy and integrity of the published manuscript.

The consent/permission was obtained from the patient for publication purposes.

ΠΕΡΙΛΗΨΗ

Στοματικές επιπλοκές λόγω χρήσης μεθοτρεξάτης από ηλικιωμένη γυναίκα

L.C. BITTENCOURT,[1] V.M. DOS SANTOS[2]

[1]Specialist in Hospital Dentistry, Brasília-DF, [2]Armed Forces Hospital and Catholic University of Brasília-DF, Brasília-DF, Βραζιλία

Αρχεία Ελληνική Ιατρικής 2025, 42(2):271–273

Σοβαρά στοματικά έλκη μπορεί να εμφανιστούν ως ανεπιθύμητη ενέργεια που προκαλείται από τη χρήση μεθοτρεξάτης. Περιγράφεται η περίπτωση μιας ασθενούς όπου η εν λόγω επιπλοκή δεν είχε διαγνωστεί πριν από τη νοσηλεία της. Η ασθενής έκανε χρήση μεθοτρεξάτης και υπέστη τραυματισμούς στο πρόσωπο λόγω πρόσφατης τυχαίας πτώσης. Επαναλαμβανόμενα στοματικά έλκη υπήρχαν μερικούς μήνες πριν και επουλώθηκαν αυτόματα, ενώ οι βλάβες εισαγωγής οφείλονταν επίσης σε διαβρώσεις οδοντικών στοιχείων που κατέστρεφαν τους μαλακούς ιστούς. Υποβλήθηκε σε χαμηλού επιπέδου laser και αντιμικροβιακές φωτοδυναμικές θεραπείες, οι οποίες ήταν σημαντικές για αναλγησία, επιταχυνόμενη αποκατάσταση και πρώιμη στοματική σίτιση. Καθώς μπορεί να εμφανιστούν στοματικά έλκη κατά τη χρήση μεθοτρεξάτης, απαιτείται περισσότερη προσοχή για την αναζήτηση εξειδικευμένης αξιολόγησης σχετικά με τις ανεπιθύμητες ενέργειες που προκαλούνται από το φάρμακο και τις αντίστοιχες θεραπείες.

Λέξεις ευρετηρίου: Ανεπιθύμητη επίδραση φαρμάκων, Θεραπεία με laser χαμηλού επιπέδου, Μεθοτρεξάτη, Στοματικά έλκη

References

1. ARCE IL, VICARI P, FIGUEIREDO VLP. Methotrexate intoxication: Diagnostic difficulty case report. *Hematol Transfus Cell Ther* 2021, 43(Suppl 1):S47–S48
2. BARROS DD, CATÃO MHC V. Evaluation of low-intensity laser photobiomodulation in the treatment of traumatic oral ulcer: An integrative literature review. *Res Soc Dev* 2022, 11:e18811427325
3. CHAMORRO-PETRONACCI C, GARCÍA-GARCÍA A, LORENZO-POUSO AI, GÓMEZ-GARCÍA FJ, PADÍN-IRUEGAS ME, GÁNDARA-VILA P ET AL. Management options for low-dose methotrexate-induced oral ulcers: A systematic review. *Med Oral Patol Oral Cir Bucal* 2019, 24:e181–e189
4. PAPAMANOLI E, KYRIAKIDOU K, KAROUSSIS IK. Low-level laser therapy in the oral cavity: A retrospection in the future. *J Cell Signal* 2022, 3:96–104
5. SCHELZEL G, PALICHERLA A, TAUSEEF A, MILLNER P. Low-dose methotrexate toxicity leading to pancytopenia: Leucovorin as a rescue treatment. *Proc (Bayl Univ Med Cent)* 2024, 37:339–343
6. SHRESTHA R, OJHA SK, JHA SK, JASRAJ R, FAUZDAR A. Methotrexate-induced mucositis: A consequence of medication error in a rheumatoid arthritis patient. *Cureus* 2023, 15:e46290
7. SANTOSO AW, SUFIAWATI I. Effectiveness of photobiomodulation in reducing pain of oral mucosal diseases: A case series. *Int Med Case Rep J* 2023, 16:407–417
8. ZHAO H, HU J, ZHAO L. The effect of low-level laser therapy as an adjunct to periodontal surgery in the management of postoperative pain and wound healing: A systematic review and meta-analysis. *Lasers Med Sci* 2021, 36:175–187

Corresponding author:

V.M. dos Santos, Hospital das Forças Armadas, Estrada do Contorno do Bosque s/n, Cruzeiro Novo, Zip code 70.658-900, Brasília-DF, Brazil
e-mail: vitorinomodesto@gmail.com