

Methotrexate induced erythema multiforme: a case report of accidental overdose

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Abstract

Methotrexate is the first-line treatment for rheumatoid arthritis (RA) and can be used in patients with systemic lupus erythematosus (SLE) with poor symptom control. In addition to reducing disease symptoms, methotrexate can cause a series of side effects, including erythema multiforme, which can affect oral mucosa and cause painful ulcerations. This article presents a case of a 39-year-old patient with an unconfirmed diagnosis of SLE that received a prescription of 10 capsules of methotrexate (2.5 mg) to be used orally once a week. However, the patient misunderstood the prescription and ingested the prescribed monthly dose in one week. She was hospitalized with multiple intraoral and extraoral lesions, intense pain and dysphagia. In addition to that, she could not take oral antibiotics and had difficulty ingesting solid food. During hospitalization, the patient was treated with topical medications and laser therapy for pain and other symptoms and was released after 9 days to continue outpatient treatment. This case report shows the importance of good communication between health care professional and patient, especially regarding the understanding of the drug prescription.

Key words: drug-related side effects and adverse reactions; erythema multiforme; mouth disease; dental care; systemic lupus erythematosus, methotrexate.

Eritema multiforme induzido por metotrexato: relato de caso de overdose acidental

Resumo

O metotrexato é o medicamento de primeira linha no tratamento da artrite reumatoide e pode ser utilizado em casos de lúpus eritematoso sistêmico quando há dificuldade no controle dos sintomas. Apesar de seu efeito no controle dos sintomas de diversas doenças, o metotrexato pode causar uma série de efeitos adversos, incluindo eritema multiforme, que é uma reação de hipersensibilidade caracterizada por úlceras dolorosas que podem afetar a pele e a mucosa oral. Esse artigo apresenta o caso de uma paciente do sexo feminino, 39 anos de idade, com diagnóstico inconclusivo de lúpus eritematoso sistêmico, que recebeu uma prescrição de 10 cápsulas de metotrexato (2,5 mg) a serem usadas por via oral uma vez por semana, sendo duas pela manhã, duas no almoço, duas no jantar, duas na manhã seguinte e duas no almoço. Entretanto, a paciente não compreendeu bem a prescrição e ingeriu toda a dose prescrita para um mês em uma semana. A paciente foi hospitalizada com múltiplas úlceras intra e extra orais, associadas a dor intensa, disfagia, dificuldade de fala entre outros sinais e sintomas, impedindo alimentação e uso de medicação por via oral. Durante a hospitalização, a paciente recebeu tratamento com medicamentos de uso tópico e laserterapia para controle da dor e da inflamação. A paciente teve alta hospitalar após nove dias de internação para continuar seu tratamento ambulatorial. Esse relato de caso mostra a importância de uma boa comunicação entre profissional de saúde e paciente, especialmente no que diz respeito à compreensão da prescrição medicamentosa.

Palavras-chave: efeitos colaterais e reações adversas relacionados a medicamentos; eritema multiforme; doenças da boca; assistência odontológica, lúpus sistêmicos; metotrexato.

Introduction

Methotrexate is a disease-modifying antirheumatic drug (DMARD) used since 1980 as the first line treatment for rheumatoid arthritis (RA).¹ Initially used as an antimetabolite medication in the treatment

of childhood leukemia, methotrexate prevents cell proliferation by inhibiting the dihydrofolate reductase enzyme.² At lower doses, an effect described as “steroid-like” has been shown in the treatment of RA and other rheumatic diseases. The mechanism of action in RA involves adenosine signaling, reduction of the expression of adhesion proteins and pro-inflammatory cytokines.¹



Although methotrexate is not the treatment of choice for systemic lupus erythematosus (SLE), its effect in controlling symptoms in patients who do not respond to hydroxychloroquine is well known.³ Adverse effects of methotrexate include ulcerative stomatitis, leukopenia, nausea, malaise, fatigue, fever, chills, dizziness, low resistance to infections and, in high doses, it usually causes erythema multiforme (EM).⁴

EM is an acute mucocutaneous immune reaction that can be triggered by infection, certain medications, or antigenic stimuli.⁵ Lesions of the oral mucosa are manifested as painful erosive blisters where thick hemorrhagic crusts can affect speech, diet and liquid intake.⁶ It can last from 3 to 6 weeks, and requires immediate discontinuation of the medication and treatment according to the severity of the signs and symptoms.⁵

Case report

A 39-year-old female patient with rheumatologic disease under investigation presented multiple ulcerations of the oral mucosa, crusts and fissures on the lips, fever, ulcerations on the hands and feet, gastralgia, dysphagia and diarrhea, making it impossible for her to eat and use oral medications, leading to her hospitalization at the University of Brasília Hospital.

In the past two years, the patient has reported arthralgia, hands, elbows and knees oedema, painful diffuse erythematous plaques, oral and genital ulcerations, alopecia and photosensitivity. She had the following diagnostic hypotheses: systemic lupus erythematosus, systemic vasculitis, and undifferentiated disease of the connective tissue, whose treatment included methotrexate, prednisone and azathioprine.

During an outpatient visit, she was prescribed a weekly oral dose of 25 mg methotrexate, with 2 capsules of 2.5 mg with each meal until 10 capsules were taken, followed by a one-week break and resumption of the regimen. However, the patient took two capsules with each meal, without any interval until completing 40 capsules, a dose that should be taken divided into four weeks. After some days, multiple extraoral and intraoral ulcerative lesions were developed, compatible with the diagnosis of EM.

On the first hospitalization day, extraoral lesions located on the nose and on the lower lip were observed, as well as intraoral ulcers on the border of the tongue and oral mucosa (Figure 1). Due to lesions in the oral cavity associated with dysphagia, diarrhea and epigastric pain, the patient was unable to ingest solid food, liquids and medications, in addition to being unable to perform oral hygiene. Lesions were also observed in the feet and hands (Figure 2).

Venous hydration therapy was initiated, as well as parenteral administration of medications. Metoclopramide 10 mg three times a day, sodium dipyron 1,000 mg every 8 hours and tramadol 100 mg every 8 hours were prescribed, in addition to the following antibiotics: ciprofloxacin 400 mg every 12 hours and clindamycin 600 mg every 6 hours intravenously due to secondary infection. Topical treatment of the oral ulcers was also performed using nystatin, aluminum hydroxide and corticosteroids. A routine of oral cleaning with 0.12% chlorhexidine digluconate solution, topical application of triamcinolone in oral base on mucosal lesions and dexpanthenol on the lips was established. Oral pasty and liquid food was maintained, which the patient ingested with some difficulty, alleviated by the application of topical anesthetic lidocaine gel 20 mg/g on the oral mucosa.

However, given the absence of a significant improvement after 3 days (Figure 3A), laser therapy was initiated (Figure 3B) to assist in the healing process. The laser applications (Therapy XT, DMC, Brazil) were performed once a day, for 5 consecutive days, using visible red light of 680 nm wavelength and infrared laser of 760 nm wavelength, with a dose of 4 J/cm² and irradiation time of 40 seconds.

On the ninth hospitalization day, the patient was discharged with significant improvement in the oral lesions and dysphagia (Figure 4) and was instructed to continue her rheumatologic monitoring.

Figure 1. (A) Ulcerations on the labial mucosa and nose; (B) Appearance of the lips and intraoral mucosa; (C) Ulceration located on the lateral border of the tongue; (D) Ulceration located on the jugal mucosa.



Figure 2. Clinical examination on the first hospitalization day. Aspect compatible with vasculitis, ulcers located in the fingers, in addition to the cyanotic aspect of the fingers



Figure 3. Partial improvement of the aspect of the oral lesions (A, B) and laser therapy (C) on the 3rd hospitalization day.

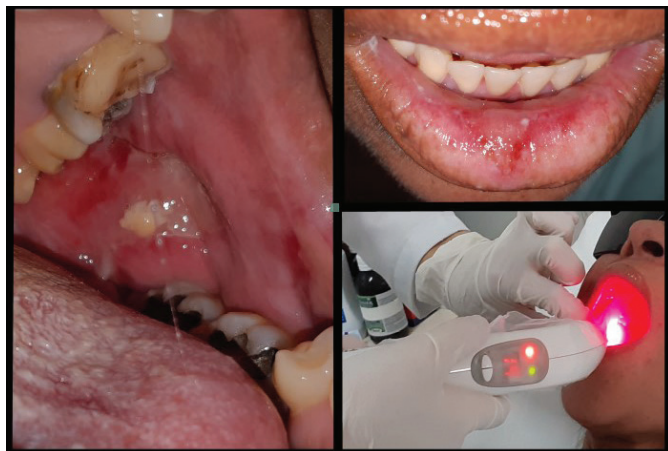


Figure 4. Clinical examination on the 9th hospitalization day, showing a significant resolution of the intraoral and extraoral lesions.



Discussion

Here we present a report of oral manifestations induced by accidental methotrexate overdose. Reports of adverse events with the use of methotrexate are not uncommon, although it is important to discuss the context in which these effects were observed. In therapeutic doses, methotrexate is an effective medication, although toxicity may be a problem for some patients.¹

We observed that, in addition to the correct prescription, it is necessary to ensure that the patient understands how to use the medication. It is important to train and empower patients to manage their medication, mainly in the management of chronic diseases.⁷ Generally, methotrexate is prescribed at a dose of 7.5 – 25 mg once a week.⁸ Unfortunately, our patient misunderstood the prescription, which ended up causing her hospitalization.

Inadequate communication between health professional and patient can be a cause of poor adherence to treatment⁷ or, as in the case presented, it can trigger a severe toxicity reaction. Although it was clear that the prescription was properly done, the patient's understanding regarding the medication dosage was inappropriate.

On the first hospitalization day, a topical use medication was prescribed for the treatment of the intraoral and extraoral lesions. As there was no significant improvement, laser therapy was recommended. A number of studies indicate the effectiveness of laser therapy for the prevention and treatment of oral mucositis that is manifested as a result of some cancer treatments.⁹ Low-intensity lasers increase cell metabolism, stimulating mitochondrial activity, acting as an analgesic and anti-inflammatory agent and repairing lesions in the mucosa.¹⁰ In the present case, the effect of laser therapy on pain relief and inflammation modulation was noticeable.

In addition to that, it is important to emphasize the contribution of the multidisciplinary team for the treatment decisions aiming at a better evolution during hospitalization. In the case in question, the dental surgeon plays a fundamental role, since oral lesions generate a significant limitation in the patient's treatment and quality of life.

Conclusion

Effective communication between health professionals and patients is essential in relation to understanding drug prescriptions for the prevention of errors related to the use of medications. The involvement of the multidisciplinary team in health can reduce risks and improve the quality of the treatment offered to the patients. In summary, the aforementioned case exemplifies the importance of communication between the health professional and the patient, as well as among the health professionals themselves.

Collaborators

ACC: Conception and design of the article, data analysis and interpretation, writing of the article, relevant critical review of the content. YPF: Conception and design of the article, data analysis and interpretation, writing of the article, relevant critical review of the content. LSV: Conception and design of the article, data analysis and interpretation, writing of the article, relevant critical review of the content. PTF: Conception and design of the article, data analysis and interpretation, writing of the article, relevant critical review of the content. DBD: Conception and design of the article, data analysis and interpretation, writing of the article, relevant critical review of the content. ENL: Conception and design of the article, data analysis and interpretation, writing of the article, relevant critical review of the content.

Patient's consent

The patient signed the Free and Informed Consent Form, through which she authorized publishing the images and description of her case.

Ethical approval

The case report herein described was approved by the Committee of Ethics in Research with Human Beings of the Medical School at the University of Brasília, under CAAE protocol 32856720.3.0000.558, and opinion No. 4,112,190, dated June 25th, 2020, observing Resolution 466/2012-CONEP/CNS and CNS Circular letter No. 166/2018.

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Authors' statement

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