

Oral Manifestations of Erythema Multiforme due to Methotrexate Intoxication

Manifestaciones Orales de Eritema Multiforme debido a Intoxicación por Metotrexato

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ABSTRACT: To report a rare case of erythema multiforme (EM) associated with methotrexate (MTX) with cutaneous and oral manifestations and to compare it to existing cases in which MTX was not used for cancer treatment. A 56-years-old female, in physical examination skin lesions and multiple oral ulcers associated with pain during manipulation were observed, and underwent treatment for rheumatoid arthritis with Methotrexate 2.5mg. During examination patient-reported that 15 days ago she had undergone a rheumatoid factor examination, doubling the MTX dosage (10mg / day) without doctor's consent. The diagnostic hypothesis of EM. The medical conduct consisted of the suspension of MTX and prescription of a vitamin complex with folic acid. Local dental therapy for to control oral lesions, pain control and lip hydration was performed using low-level laser therapy (Twin Laser, P: 40mW, T: 50s, DE: 50J / cm), benzydamine hydrochloride spray, purified lanolin for lip dryness, and toothpaste without sodium lauryl sulfate to prevent burning. After 12 days, there was significant remission of oral and skin signs and symptoms, which confirmed the diagnosis was EM due to MTX intoxication. Thorough clinical evaluation and anamnesis favored diagnosis and early multi-professional management provided remission of oral and skin lesions, prevented systemic complications.

KEY WORDS: erythema multiforme. methotrexate. stomatitis. mucositis. oral manifestations.

INTRODUCTION

Erythema multiforme (EM) is a mucocutaneous condition with higher prevalence in young adults, with a predilection for males and can be classified into major EM and minor EM. Clinically, it is characterized by ulcerations in the oral mucosa, causing painful symptoms, which, with the worsening of the disease, can progress to diffuse desquamation and ulcerations in all skin and mucous membranes (Samin *et al.*, 2013).

The pathophysiology of EM involves antigen-antibody mechanisms, and, in most cases, it may be related to infection by the herpes simplex virus, however, other factors, such as some medications, can trigger it (Samin *et al.*). Methotrexate (MTX) is a folic acid antagonist medication, used to treat several

diseases such as rheumatoid arthritis and neoplasms, which, despite presenting satisfactory therapeutic results, triggers several adverse reactions, including EM (Samin *et al.*; Sanchis *et al.*, 2010). The skin ulcers and erythema are frequent in EM or Stevens Johnson Syndrome (SJS) related to the MTX. But the literature showed few cases of oral ulcers in patients receiving MTX and causing EM, they are more frequent when related to SJS (Hani *et al.*, 2000).

The present article aims to report a case of EM associated with MTX with cutaneous and oral mucosa manifestations, applied therapy, and through a brief review of the literature, to compare it with existing cases in which MTX was not used in the treatment of cancer patients.

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CASE REPORT

The participant gave her informed consent for her participation in the study. The study was approved by the Human Research Ethics Committee (CAEE 35405220.0.0000.5417).

A 56-years-old female, white, nurse, presented with extensive ulcers on the lower lip asymptomatic. In the history of the current disease, the patient reported that the lesion appeared 5 days after suffering a lip burn from the ingestion of hot liquid, followed by burning mouth during oral hygiene and eating only with liquid and pasty diet. In the medical history, the patient reported being under medical treatment for rheumatoid arthritis and hypothyroidism, using Methotrexate 2.5mg and Levothyroxine 0.25mg. On extraoral physical examination, presented good general conditions and cutaneous erythematous lesions, generalized brown spots, and crusts, which appeared concomitantly with intraoral lesions (Fig. 1).

Clinically, extensive ulcers were found on the lip and lower lip mucosa, bilateral buccal mucosa, inserted gingiva, tongue, floor of mouth, hard and soft palate associated with painful sensitivity during manipulation. During the clinical examination, the patient reported

that she had undergone a rheumatoid factor examination 15 days ago and, when analyzing the result, noticed changes. Therefore, without doctor's consent, she doubled the dosage of MTX, totaling a dose of 10 mg daily.

The therapeutic approach consisted of supportive and complementary symptomatological treatment for oral lesions, through low-level laser therapy in a single session (Twin Laser, P: 40 mW, T: 50s, DE: 50J / cm) and benzydamine hydrochloride spray, three times a day, ten minutes before meals, to create comfort during feeding; purified lanolin for lip dryness every 6 hours and toothpaste free of sodium lauryl sulfate, to prevent burning during oral hygiene. The patient was referred to the rheumatologist to adjust the MTX dosage.

In the 5-day follow-up, the symptoms improved, and the patient reported that the rheumatologist suspended the use of MTX for 30 days and prescribed a vitamin complex with folic acid. On physical examination, an important reduction in the size and quantity of ulcers was observed (Fig. 2), maintaining oral care procedures, prescription of benzydamine hydrochloride spray, purified lanolin, and toothpaste free of sodium lauryl sulfate.



Fig. 1. An erythematous lesion and crusted on the right eyebrow and hand. Lower lip with ulcers with yellowish-white pseudomembrane and intraoral ulcers.

After 12 days the patient had no painful symptoms. Clinically, the lesions were completely remitted in the entire oral cavity, but with an erythematous region on the lower lip and slightly dry lips (Fig. 3). There was also a complete remission of the cutaneous lesions. The therapeutic approach then consisted of suspending the analgesic and topical anesthetic solution and maintaining the lip moisturizer and toothpaste for oral hygiene that is not aggressive to the mucous membranes. There was no need to perform a biopsy of the oral mucosa since there was complete remission of the lesions after medical and dental procedures. Based on that information, the final diagnosis of Erythema Multiforme resulting from drug intoxication by MTX was reached.



Fig. 2. Ulcers in the healing process on the lower lip.



Fig. 3. Lower lip slightly dry and erythematous. Total remission of lesions in the left upper labial mucosa.

DISCUSSION

The oral ulcers as manifestations of EM related to MTX are rare and there is not one case reported in the literature. Despite this condition, a study showed 6.2 % of oral ulcers in patients receiving MTX (Magdy & Ali, 2021), but there is no information as to this resulting in EM. These considerations made this case report relevant to physicians, nurses and dentists to diagnose and treat patients with oral ulcers and EM.

Studies have shown a higher prevalence of EM in young adult men (20 to 40 years) (Hani *et al.*, 2000; Blanes *et al.*, 2005; Sanchis *et al.*, 2010; Celenano *et al.*, 2015; Kechichian *et al.*, 2018; Magdy & Ali, 2021), however, in the current clinical case and most cases of EM associated with the use of MTX used in Table I (9/11), were women over the age of 50 (Omeregje *et al.*, 2011; Troeltzsch *et al.*, 2013; Jimbu & Demitsu, 2014; Lee *et al.*, 2015; Katsoulas *et al.*, 2016; Nam, 2018). Certainly, cases of EM associated with the use of MTX in women and older age groups may be related to a higher incidence of arthritis and psoriasis in adult women, in addition to the fact that the elderly population has more comorbidities and uses a greater amount of medication. It is common to find an association between EM and comorbidities such as polyarthritis (Lee *et al.*, 2015), rheumatoid arthritis (Blanes *et al.*, 2005; Omeregje *et al.*, 2011; Troeltzsch *et al.*, 2013; Jimbu & Demitsu, 2014; Lee *et al.*, 2015; Katsoulas *et al.*, 2016; Nam, 2018), related case.

The cellular immune response is the main cause of EM, being infection by the Herpes simplex virus, followed by *Mycoplasma pneumonia* as the most relevant, about 82 % of cases (Kechichian *et al.*, 2018). Since medicated drugs are triggering factors that affect less than 10 % of cases (Samim *et al.*, 2013), with no survey by Sanchis *et al.* (2010) reduced a rate of 27 % (6/22) of cases, and were not performed by Celentano *et al.* (2015) the rate was 46.7 % (28/60).

In the present case, we consider that the use of the exaggerated dose of MTX was the factor that triggered EM, as in the other cases mentioned in the literature (Table I). Other drugs related to the onset of EM are non-steroidal anti-inflammatory drugs, antibiotics, antifungals, and antivirals (Celentano *et al.*, 2015).

The clinical manifestations of EM in the oral mucosa are diverse and correspond to the region most affected (25 % to 70 %), and it is often the only affected

site (Sanchis *et al.*, 2010). In the current case, the patient presented with extensive ulcers with irregular margins and an erythematous halo with a pseudomembranous surface on the lower lip, buccal mucosa, inserted gingiva, tongue, floor of the mouth, soft and hard palate that characterized the clinical manifestations of EM. The cutaneous lesions of EM are characterized by ulcers, brown spots (hyperpigmented), erythematous papules, or macules with whitish halos forming symmetrical target-type lesions (Samim *et al.*, 2013) as seen in this case.

Erythema multiforme minor (EMm), is more prevalent and is characterized by the involvement of the mucosa (oral mucosa) and skin (50 %), and when it also affects other mucous membranes, such as the ocular, genital or nasal, it becomes known as erythema multiforme major (Stevens-Johnson syndrome) (36.4 %) (Sanchis *et al.*, 2010; Samim *et al.*, 2013). Therefore, the mucocutaneous involvement of this case corroborates the classic clinical presentation of EM caused by the use of MTX (Sanchis *et al.*, 2010; Omoregie *et al.*, 2011).

The presence of fever, malaise, and weakness are prodromal signs of EM. Oral pain is commonly reported and can lead to odynophagia, dysphagia, significant malnutrition, and hospitalization for support may be necessary (Troeltzsch *et al.*, 2013). The patient in this case only mentioned burning mouth 5 days after suffering possible burns and pain during the manipulation of the oral mucosa because she believed that this was the cause of the oral manifestations, but was eating normally, which made the clinical picture favorable to rapid recovery.

In view of the similarity of the mucocutaneous clinical manifestations to other diseases, such as autoimmune disorders, pemphigus vulgaris and paraneoplastic pemphigus, benign mucous membrane pemphigoid, oral lichen planus, allergic reactions, celiac disease, viral and bacterial infection, it is essential to perform the differential diagnosis, and, in the case of EM, the detailed clinical examination associated with careful anamnesis are essential to identify the causative factor associated with typical clinical characteristics leading to the correct diagnosis, and often dispense with eventual unnecessary biopsies (Troeltzsch *et al.*, 2013).

It is known that MTX is used in the treatment of several diseases and toxicity with mucocutaneous manifestation, will occur depending on the patient's tolerability and predisposition of the dose, regardless

of the underlying disease being treated, such as arthritis, psoriasis or malignant neoplasms (Talacko *et al.*, 2010). These circumstances can lead to confusion in the use of terminology and diagnosis of EM since the terms stomatitis and mucositis are used to refer to cases with a clinical aspect compatible with EM (Castaño *et al.*, 2005; Farthing *et al.*, 2005; Talacko *et al.*, 2010; Jimbu & Demitsu, 2014). The terminologies stomatitis and mucositis are used to designate several inflammatory oral lesions, such as traumatic ulcers, thrush and the term oral mucositis is recommended by some authors to describe oral lesions resulting exclusively from the cytotoxicity of antineoplastic treatment (Castaño *et al.*, 2005; Farthing *et al.*, 2005; Talacko *et al.*, 2010).

The lack of standardization of the terms EM, stomatitis, and mucositis, as seen in Table I, makes it difficult to establish a concise communication between health professionals and researchers. Therefore, we suggest the use of the term erythema multiforme for oral lesions resulting from the use of high doses of MTX to treat systemic diseases except for antineoplastic treatment, and in this case, we suggest using the term oral mucositis.

The cure of EM is spontaneous after the dose reduction or suspension of MTX, and the lesion remission time varies between 2 to 3 weeks in minor EM, and up to 6 weeks in cases of major EM, and there is no specific treatment as well established, but supportive care and control of secondary infections are important (Samim *et al.*, 2013). Table I shows that remission of EM occurred within 7 to 60 days, with 50 % of the cases resolving the lesions within 12 to 14 days, regardless of local treatments performed with the use of anti-inflammatory, anesthetic, topical analgesic, and low-power laser therapy. This shows that the remission of EM occurred by suspending the use of MTX and other complementary treatments such as application of anti-inflammatory and topical anesthetic, low-level laser therapy reduced oral pain during follow-up even in the presence of ulcers.

An important factor that must be taken into account is that the patient's self-medication, even though she is a health professional, was determinant in the toxicity of MTX and manifestation of EM. The practice of self-medication is common among patients with arthritis, mainly in the search for pain control, exposing them to a greater risk of drug interactions, adverse effects, and toxicity (Bagatini *et al.*, 2011). Therefore, patients who use MTX should be instructed

Table 1. Data extracted from other published studies on erythema multiforme.

Author	Blanes <i>et al.</i>	Omoregie <i>et al.</i>	Troeltzsch <i>et al.</i>	Jimbu & Demisu	Lee <i>et al.</i>	Lee <i>et al.</i>	Lee <i>et al.</i>	Lee <i>et al.</i>	Katsoubas <i>et al.</i>	Nam	Present case
Year	2005	2011	2013	2014	2015	2015	2015	2015	2016	2018	2019
Patient Age (years)	74	60	71	71	77	71	68	73	77	77	56
Sex	F	M	F	M	F	F	F	F	F	F	F
Comorbidity treated with MTX	Seronegative polyarthritis	RA	RA	RA	RA	RA	RA	RA	RA	RA	RA
Other Comorbidities	NR	NR	CHF	SAH, PH, CD	NR	CRF, SAH, right hemiplegia	OSP	OSP	OSP	No	HT
MTX dose	20 mg 1x/week	15 mg 1x/week	25 mg 1x/week	8 mg 1x/week	17.5 mg 1x/week	10 mg 1x/week	15 mg 1x/week	2.5 mg 1x/week	2.5 mg 1x/week	7.5 mg 1x/week	2.5mg daily
Other Medicines	Ibuprofen Naproxen Omeprazole Folic Acid	NR	Citalopram (20 mg) Clopidogrel	NR	Prednisolone Leflunomide Celecoxib Rebamipide Rebeprazole	Sulfasalazine Methylprednisolone Bisoprolol fumarate Hydrochlorothiazide Esomeprazole magnesium Bisylate Atorvastatin calcium	Folic acid Leflunomide Rebamipide Alprazolam Celecoxib Acetaminophen (325 mg) Tramadol HCL (37.5 mg) Hydrochlorothiazide Calcium carbonate (1,250 mg) Cholecalciferol (1,000 IU) Atorvastatin calcium Fimasartan potassium trihydrate Tenipalate	Folic acid (5 mg), Prednisone (5 mg) 5-courses of rituximab IV 1x/week	Folate Prednisobone Celecoxib	Levothyroxine (0.25 mg)	
Oral Manifestations	NR	Pain, Ulcers with necrotic tissue (lower lip)	Inflammation, Pain, Ulcers (buccal mucosa, alveolar crest), Multiple lichenoid lesions (floor of the mouth)	Ulceration (floor of the mouth)	Sensitivity (oral mucosa)	Ulcers, Erythematous lesions (labial and oral mucosa)	Ulcers, Erythematous lesions (lip, tongue, oral mucosa) with bleeding tendencies	Ulcers (lower lip, buccal mucosa, and inserted gingival)	Ulcers (hard palate, oral cavity)	Ulcers (lower lip, buccal mucosa, and inserted gingival)	
Extraoral Manifestations	Rash (trunk/ extremities) with macules and papules Positive Nikolsky's sign (no blisters)	Bullous eruptions (upper/lower extremities)	Cutaneous ulcer (right groin)	NR	NR	NR	NR	Ulcers (tongue, lower lip, alveolar maxillary/mandibular mucosa), Atypical ulcers (dorsal surface of the tongue, lower lip mucosa)	NR	NR	Erythematous cutaneous lesions, Generalized brown spots/crusts
Type of intervention	Oral/topical corticosteroids, AI medication removed	MTX removed	Hospitalized patient, MTX removed	Corticosteroids, MTX dose reduction (2mg/week)	Folic acid 1mg (1x/day), MTX removed	MTX dose reduction (5 mg/1x/week)	Hospitalized patient (hematological and renal problems), MTX removed	MTX removed	MTX removed	MTX removed	Low-level laser therapy, Benzidamine hydrochloride spray (3x/day), Lanolin cream, Sodium lauryl sulfate-free toothpaste, MTX removed
Evolution	Complete resolution after 14 days	Complete resolution after 12 days	Complete resolution after 30 days	Complete resolution (time not related)	Complete resolution after 14 days	Complete resolution after 14 days	Complete resolution after 21 days	Complete resolution after 21 days	Complete resolution after 30 days	Complete resolution after 12 days	Complete resolution after 12 days
Term used to describe injuries	EM	EM	OM	OMU	OM	OM	OM	US	OM	OM	EM

Legend: F=female; M=male; RA= rheumatoid arthritis; NR= not related; SAH= systemic arterial hypertension; CHF= congestive heart failure; PH= prostatic hyperplasia; CD=cardiac disease; HT=hypothyroidism; MTX= methotrexate; CRF= chronic renal failure; OSP=osteoporosis; EM= erythema multiforme; OM=oral mucositis; OMU= oral mucosal ulceration; US= ulcerative stomatitis

on the severity of the adverse effects of self-medication and consider that they are multi-drug patients, increasing the chances of drug interactions and toxicity.

Regular medical follow-up should be directed in order to control the systemic disease with tolerable doses, not least because, in addition to EM, MTX can lead to other serious renal, hepatic and myelosuppression adverse effects, which may increase the risk of secondary infections and higher morbidity (Sanchis *et al.*, 2010; Troeltzsch *et al.*, 2013).

Early diagnosis and management of EM due to MTX toxicity, provided remission of oral and skin lesions, and control of oral pain, which prevented more serious systemic complications. There are controversies regarding the terms used to designate erythema multiforme, which hinders communication between professionals and researchers. Therefore, the importance of a thorough clinical evaluation for the diagnosis and use of terminology, erythema multiforme, is emphasized to describe the oral lesions resulting from MTX intoxication.

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CARVALHO, C. G.; TERRABUIO, B. R.; MOURA, L. L.; MANZANO, B. R.; SIMPIONE, G.; CAMINHA, R. D. G.; SANTOS, P. S. S. Manifestaciones orales de eritema multiforme debido a intoxicación por metotrexato. *Int. J. Odontostomat.*, 16(2):195-201, 2022.

RESUMEN: El objetivo de este trabajo fue informar un caso raro de eritema multiforme (EM) asociado a metotrexato (MTX) con manifestaciones cutáneas y orales y compararlo con casos existentes en los que no se utilizó MTX para el tratamiento del cáncer. Caso clínico: Mujer de 56 años, en el examen físico se observaron lesiones cutáneas y múltiples úlceras de la cavidad oral asociadas a dolor durante la manipulación. Se sometió a tratamiento para la artritis reumatoide con metotrexato 2,5 mg. Durante el examen, la paciente informó que hacía 15 días se había sometido a un examen de factor reumatoide, duplicando la dosis de MTX (10 mg / día) sin el consentimiento del médico. La hipótesis diagnóstica de EM. La conducta médica consistió en la suspensión de MTX y prescripción de un complejo vitamínico con ácido fólico. La terapia dental local para el control de las lesiones orales, el control del dolor y la hidratación de los labios se realizó mediante terapia con láser de bajo nivel (Twin Laser, P: 40mW, T: 50s, DE: 50J / cm), aerosol de clorhidrato de bencidamina, lanolina purificada para la sequedad de labios y pasta de dientes sin lauril sulfato de sodio para evitar

quemaduras. Después de 12 días, hubo una remisión significativa de los signos y síntomas orales y cutáneos, lo que confirmó el diagnóstico de ME por intoxicación por MTX. La evaluación clínica exhaustiva y la anamnesis favorecieron el diagnóstico y el manejo multiprofesional precoz proporcionó la remisión de las lesiones orales y cutáneas, evitando además complicaciones sistémicas.

PALABRAS CLAVE: eritema multiforme. metotrexato. estomatitis. manifestaciones de la cavidad oral.

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