



A Double-Edged Puzzle: Diagnostic Challenges in Herpes-Triggered Erythema Multiforme and Methotrexate Oral Toxicity

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Case Report

History

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ABSTRACT

Erythema multiforme (EM) is an acute immune-mediated mucocutaneous disorder most commonly triggered by infections, particularly herpes simplex virus, or less frequently by medications. Diagnostic differentiation becomes challenging in patients receiving long-term immunosuppressive therapy. This report describes a 56-year-old female on chronic methotrexate therapy for rheumatoid arthritis and fibromyalgia who presented with sudden-onset, painful oral ulcerations without cutaneous involvement or prodromal viral symptoms. Clinical examination revealed ulcerative lesions involving the buccal mucosa and tongue. Drug-induced EM (DIEM) was considered as a differential diagnosis; however, the lesions demonstrated progressive resolution following antiviral therapy with acyclovir and topical corticosteroids, despite continued methotrexate use. Laboratory investigations showed elevated erythrocyte sedimentation rate (ESR) and neutrophilia, indicating an active inflammatory process. The favourable clinical course, absence of lesion progression with ongoing methotrexate therapy, and response to antiviral treatment supported a probable diagnosis of herpes simplex virus-associated erythema multiforme (HAEM). This case highlights the importance of careful clinical assessment, consideration of confounding medications, and cautious interpretation of therapeutic response to avoid unnecessary discontinuation of essential immunosuppressive therapy.

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Introduction

Erythema multiforme (EM) is an acute, immune-mediated condition characterised by target-shaped skin lesions, sometimes accompanied by mucosal involvement, and is often triggered by infections, most commonly herpes simplex virus or, less frequently, by drugs.¹ EM is most commonly triggered by infections, particularly Herpes Simplex Virus (HSV), though it may also be induced by medications and autoimmune conditions.² Clinically, EM is classified into EM minor (target lesions without mucosal involvement), EM major (skin and mucosal lesions), Stevens-Johnson syndrome (widespread blistering with mucosal erosions), and toxic epidermal necrolysis (severe skin detachment involving >30% of the body surface).³

In HSV-associated erythema multiforme (HAEM), fragments of the virus are carried to the skin by immune cells, where they trigger CD4+ T cells to release interferon-gamma (IFN- γ), causing inflammation. In contrast, drug-induced Erythema multiforme (DIEM) involves TNF- α and direct damage to skin cells (keratinocyte apoptosis), often due to the buildup of reactive drug byproducts in people with slower drug metabolism. Medications such as methotrexate have been implicated, where drug toxicity can precipitate EM through similar apoptotic mechanisms. Severe forms like Stevens-Johnson

syndrome also involve Fas-FasL-mediated cell death. EM minor is linked to immune complex deposition and blood vessel inflammation (a type III hypersensitivity reaction), while EM major may involve autoantibodies targeting skin cell proteins. Some people, especially those with the HLA-DQ3 gene type, are genetically predisposed to recurrent EM.³

EM is an acute mucocutaneous condition that may present with both cutaneous and mucosal lesions, although mucosal sparing is not uncommon in milder forms. A thorough clinical evaluation should consider possible triggers such as infections, medications, or constitutional symptoms. In the EM minor, prodromal symptoms are typically mild or absent but may include fatigue, malaise, or features of an upper respiratory tract infection. In contrast, an EM major may begin with more prominent systemic symptoms like fever, cough, sore throat, generalised aches, vomiting, and diarrhoea, especially in cases associated with *Mycoplasma pneumoniae*. These symptoms may precede the rash by up to two weeks.¹

The hallmark cutaneous lesion of erythema multiforme is the target or iris lesion, characterised by three concentric zones comprising a central dusky or blistered area, a paler oedematous ring, and an outer

erythematous rim. Lesions are typically round, symmetrically distributed, and preferentially involve the extensor surfaces of the limbs, palms, soles, and dorsal aspects of the hands and feet, with relative sparing of the trunk. Atypical lesions with irregular morphology and fewer zones may also be observed.¹ Among the various triggers implicated in erythema multiforme, HSV infection is considered one of the most common predisposing factors and has been identified in up to 70% of diagnosed cases.²

This case report highlights the diagnostic challenges of EM in patients on long-term immunosuppressive therapy such as methotrexate. Oral ulcerations in such individuals may mimic drug-induced toxicity but can also represent HAEM or other infection-related manifestations. Distinguishing between these causes is critical, as discontinuing methotrexate may destabilise systemic disease, while missing an infectious trigger delays appropriate treatment. By documenting the clinical course and favourable response to antivirals despite continued methotrexate, this case emphasizes the importance of therapeutic response in refining diagnosis and guiding safe management.

Case Report

A 56-year-old female presented to the outpatient department clinic with complaint of multiple painful ulcers in the right cheek and tongue region for the past 7 days. The ulcers were sudden in onset and initially presented as small, red spots that progressively enlarged and coalesced, forming larger ulcerative lesions with surrounding erythema. The patient noted that the lesions subsequently developed a whitish film over the surface. The ulcerations were associated with a burning sensation and pain during food intake, which interfered with her ability to eat and speak comfortably.

The patient had a known medical history of type 2 diabetes mellitus and hypertension. She had been treated with glimepiride-metformin (1 mg + 500 mg) twice daily

and telmisartan 40 mg once daily for the past three years. The patient reported having received a short course of linezolid (600 mg twice daily for 5 days) for an upper respiratory tract infection approximately one year prior, and the same antibiotic was re-prescribed for a similar indication during the current episode. The patient reported a two-year history of methotrexate therapy (10 mg each after lunch and dinner, once a week) prescribed for rheumatoid arthritis and fibromyalgia. The patient also reported an adverse oral habit in the form of occasional khaini use (a form of chewable tobacco) during the same period, with no history of fever, prodromal viral symptoms, or extraoral manifestations such as skin lesions or lymphadenopathy.

Intraoral examination revealed poor oral hygiene, with generalised attrition, Grade II gingival recession, and missing teeth (16, 21, 36, and 37 according to the FDI tooth numbering system). A large ulcerative lesion was noted on the right buccal mucosa, extending anteroposteriorly from the mandibular second premolar to the distal aspect of the second molar, measuring approximately 2.5 × 1.2 cm. The lesion appeared erythematous with ulceration, surrounded by a reddish halo and mild hyperpigmentation (Figure 1a).

A solitary ulcer was also observed on the right lateral border of the anterior two-thirds of the tongue, extending slightly onto the ventral surface. This lesion measured approximately 2.0 × 0.8 cm, presented with a yellowish-white necrotic floor, and had slightly raised and rolled margins surrounded by inflamed mucosa (Figure 1b). The ventral surface of the tongue showed diffuse erythematous areas with irregular margins, involving a region approximately 2.5 × 1.5 cm. Notably, a whitish elevated patch was seen along the midline of the ventral tongue, measuring about 0.8 × 0.5 cm, which was well-demarcated, non-scrapable, and slightly raised (Figure 1c). At her first visit, a provisional diagnosis of HAEM was made based on multiple acute oral ulcers. Informed written consent was obtained from the patient.



Figure 1. Clinical manifestation of the intra-oral lesion at the first visit. a) Retromolar trigone and vestibular mucosa, b) Lateral border of the tongue, and c) Ventral surface of the tongue.

Treatment and Methods

Given her history of long-term methotrexate therapy for rheumatoid arthritis and fibromyalgia, methotrexate-induced erythema multiforme was also considered as a differential diagnosis. Blood investigations, including complete blood count (CBC), serology tests for HSV, erythrocyte sedimentation rate (ESR), and fasting blood sugar (FBS), were advised. She was prescribed acyclovir

400 mg three times daily after meals, clobetasol propionate 0.05% ointment for topical application over the lesions with instructions to retain for 15–20 minutes and then rinse without swallowing, a corticosteroid mouthwash prepared by dissolving a crushed 10 mg prednisolone tablet in 30 mL of water to be used as a swish-and-spit rinse, and sucralfate suspension administered 10 minutes before meals for symptomatic

relief, for a duration of 7 days. The patient was referred to the Department of Rheumatology for further evaluation and was recalled after 7 days for follow-up.

Treatment Outcome, Follow-up, and Result

On her second visit, despite continued methotrexate use, clinical examination revealed approximately 50% remission of the oral lesions in the buccal mucosa and the lateral border of the tongue, and complete remission on the ventral surface of the tongue (Figure 2a-2c). Blood tests revealed elevated ESR (50 mm/hr), mild anaemia (Hb 11.2 g/dL), neutrophilia (72%), and elevated fasting blood glucose levels (346 mg/dL), indicating ongoing

inflammation and poor glycaemic control; in addition, HSV serology was positive.

At her third follow-up visit on clinical examination, approximately 90% remission of the oral cavity lesions was noted (Figure 3a-3c). Based on the clinical course, favourable response to antiviral therapy, and lack of lesion progression despite continued methotrexate therapy, HAEM was considered the most likely clinical diagnosis. The patient was advised to continue topical corticosteroid therapy along with the prednisolone mouthwash as per previous instructions, while acyclovir and sucralfate suspension were discontinued, and was scheduled for review after one month.



Figure 2. Clinical manifestation of the intraoral lesion during the 2nd follow-up. a) Retromolar trigone and vestibular mucosa, b) Lateral border of the tongue, and c) Ventral surface of the tongue.



Figure 3. Clinical manifestation of the intra-oral lesion during the 3rd follow-up. a) Retromolar trigone and vestibular mucosa, b) Lateral border of the tongue, and c) Ventral surface of the tongue.

Discussion

This case highlights the diagnostic complexity of acute oral ulcerations in patients receiving immunosuppressive therapy. Although methotrexate-associated EM was initially considered, the absence of dose escalation or systemic toxicity, the oral-limited and self-limiting course, and the lack of lesion progression despite continued methotrexate use argue against a drug-induced aetiology. In contrast, the clinical presentation and favourable response to antiviral therapy and positive HSV serology were more consistent with HAEM; however, the absence of confirmatory virological or histopathological investigations and the concurrent use of corticosteroids remain important limitations. Overall, this report supports a probable diagnosis of HAEM and emphasises the need for cautious interpretation of therapeutic response and objective diagnostic testing where feasible.

The concomitant administration of linezolid represents an additional diagnostic confounder. Although linezolid is not a common trigger for erythema multiforme, rare mucocutaneous adverse drug reactions have been documented. Tirú-Vega et al.⁴ reported a middle-aged patient who developed a purpuric drug eruption temporally associated with linezolid therapy,

with lesion resolution following drug withdrawal, supporting a causal relationship between linezolid exposure and cutaneous inflammation. Similarly, Prathap et al. described a patient who developed a well-defined fixed drug eruption shortly after initiation of linezolid, with recurrence upon re-exposure, further confirming its potential to induce mucocutaneous hypersensitivity reactions.⁵ These reports highlight the importance of considering antibiotic-related mucocutaneous toxicity when evaluating acute oral ulcerations, particularly in medically compromised patients receiving multiple systemic medications. Nevertheless, in the present case, prior tolerance to linezolid and the absence of lesion progression despite its continuation during the current episode, together with the favourable clinical course, reduce the likelihood of linezolid as the primary aetiological factor.

The elevated ESR observed in this patient further supports the presence of an active systemic inflammatory process but lacks disease specificity. It is a routine hematologic marker that increases in response to diverse inflammatory and immune-mediated conditions but does not reliably distinguish among specific aetiologies. Therefore, ESR should be interpreted as a supportive

indicator of inflammation in the clinical context rather than as a definitive diagnostic marker. In this case, the raised ESR corroborated an inflammatory aetiology but could not independently differentiate between infectious, drug-induced, or immune-mediated mechanisms.⁶

In contrast, published methotrexate-associated erythema multiforme cases typically occur following dosage errors or escalation rather than stable long-term therapy. A 39-year-old woman developed extensive oral and cutaneous lesions after accidental methotrexate overuse, with resolution only after drug withdrawal and supportive care.⁷ Similarly, a 56-year-old female developed oral and skin ulcerations after an unauthorised dose increase, resolving after methotrexate cessation and folinic acid therapy.⁸ Unlike the present case, these reactions required modification or discontinuation of methotrexate, supporting a dose-dependent drug aetiology distinct from HAEM.

The use of concomitant antiviral therapy and corticosteroids in the present case is consistent with management strategies reported in recent literature. Dharel et al.² described an oral-predominant variant of HAEM that demonstrated clinical improvement following systemic acyclovir in combination with supportive corticosteroid therapy, illustrating reported management approaches that combine antiviral treatment with adjunctive inflammatory control. Similarly, Muryah et al.⁹ reported successful resolution of HAEM with combined acyclovir and corticosteroid treatment, underscoring that anti-inflammatory therapy is frequently used adjunctively rather than as a sole intervention. In the present case, despite the confounding effect of concurrent corticosteroid use, the overall clinical course, absence of lesion progression with continued methotrexate therapy, and favourable response to antiviral treatment collectively support HAEM as the most plausible diagnosis.

Conclusions

In this patient, the clinical presentation, favourable response to antiviral therapy, and supportive immunopathogenic evidence from the literature favoured a diagnosis of HAEM. The absence of lesion progression despite continued methotrexate therapy reduced the likelihood of a drug-induced aetiology. From an immunologic perspective, HAEM is predominantly mediated by IFN- γ -driven CD4⁺ Th1 responses to viral DNA, in contrast to the tumour necrosis factor- α and CD8⁺ cytotoxic T-cell predominance described in DIEM. Although laboratory findings such as elevated ESR and neutrophilia were non-specific, they supported an active inflammatory process. Taken together, these findings support a probable diagnosis of HAEM and highlight the importance of careful clinicopathologic correlation to avoid unnecessary modification of essential immunosuppressive therapy.

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Conflicts of Interest Statement

No conflicts of interest.

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