CASE REPORTS

Rare presentation of drug-induced oral erythema multiforme and its management: a case report

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ABSTRACT

Aim. This case report discusses a rare variant of drug-induced erythema multiforme, focusing on its clinical features, diagnosis, and management.

Background. Drug-induced erythema multiforme (DI-EM) is a hypersensitivity reaction occurring due to exposure to certain medications. DI-EM typically presents as erythematous and painful lesions on the oral mucosa, including the lips, tongue, and buccal mucosa.

Case description. A 42-year-old male was referred to the Oral Medicine clinic with a chief complaint of painful lip ulceration and eruptions on the body after consuming medications. A detailed history was taken, and after a thorough examination, a perilesional biopsy for histopathological and immunopathological tests was performed. Following the exclusion of all other conditions with a similar presentation, a diagnosis of drug-induced erythema multiforme (DI-EM) was established.

Conclusion. DI-EM can pose a diagnostic challenge due to its presentation. However, a diagnosis can be established by excluding other conditions associated with chronic inflammation or the formation of vesicles or bullae.

Clinical Significance. DI-EM is a rare variant of EM with a very low prevalence in the general population, making it a challenging condition to diagnose due to its similarity in presentation with other mucocutaneous disorders. A thorough medical history, along with histopathology and immunology tests, coupled with ruling out other diseases and noting a positive history of recent drug consumption, aids in recognizing this condition, given the absence of any confirmatory diagnostic test. Early diagnosis and cessation of causative drugs, along with supportive medications, contribute to the complete resolution of the condition.

Keywords: drug-induced erythema multiforme, EM diagnosis, EM variants, herpes associated erythema multiforme

INTRODUCTION

Erythema multiforme (EM) is an uncommon, acute inflammatory condition that impacts both the mucosa and skin, presenting in various manifestations. It spans from a self-limiting, acute generalized exanthematous subtype with minimal oral involvement known as erythema multiforme minor (EM minor), to a more severe, progressive subtype characterized by widespread mucocutaneous necrosis of epithelial cells, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). EM major falls in between in terms of severity [1]. This condition is more prevalent among teenagers and young adults, with a higher inclination towards males [2].

DI-EM, a hypersensitivity reaction triggered by certain medications, typically manifests as skin and
mucous membrane rashes or lesions. Its severity varies from mild to severe, including the development of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Drug-associated EM is infrequent, accounting for less than 10% of cases [3]. A wide range of drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), barbiturates, cephalosporins, estrogens, phenothiazines, progestrones, protease inhibitors, sulphonamides, sulphonylurea derivatives, and tetracyclines, can induce DI-EM. Distinguishing drug-induced EM from other causes may pose clinical challenges [4].

In over 80% of instances, infections stemming from Herpes simplex virus (HSV) 1 and 2 serve as the primary triggers, followed by Epstein-Barr virus (EBV) and Mycoplasma pneumoniae [5]. Additional factors, including various drugs like nonsteroidal anti-inflammatory drugs, antibiotics, and anticonvulsants, can also induce the condition [6]. The pathogenesis of drug-induced erythema multiforme (DI-EM) involves an immune-mediated response to the drug, leading to the generation of cytotoxic T cells and activation of inflammatory mediators, causing damage to the skin and mucous membranes. Approximately 70% of recurring EM cases are linked to a prior infection caused by the herpes simplex virus [7]. Antigens induced by certain medications or viral infections prompt apoptosis of Keratinocytes through a hypersensitivity reaction triggered by Cytotoxic T lymphocytes [8]. The primary management approach for EM involves providing symptomatic relief with topical and systemic steroids while avoiding known triggers such as specific drugs [9].

DI-EM poses diagnostic challenges as it mimics various mucocutaneous conditions. Typically, the diagnosis relies on the clinical presentation, drug exposure history, and confirmation through perilesional biopsy to rule out alternative causes. A variant known as drug-induced oral erythema multiforme (DI-OEM) manifests with exclusively oral lesions, usually without skin involvement. In the case reported here, the patient exhibited drug-induced EM with lesions affecting the skin around the neck and chest.

CASE HISTORY

A 42-year-old male from Najran, KSA, was referred to the Oral Medicine clinic in September 2022 with a chief complaint of painful ulcers on the lips and oral cavity associated with a burning sensation for two weeks. Previously, the patient was screened at a primary health care center, where he presented a complaint of a sore throat and was prescribed broad-spectrum antibiotics: Erythromycin (250mg 2×/day) and Amoxicillin (625mg 3×/day). The patient continued to consume the antibiotics for over two weeks, after which he developed lip ulcers and was referred to the Dental center. The patient was medically fit with no known history of allergies to any medication, and there was no past dental or oral habit history.

Signs and symptoms of present illness

The patient generally experienced fatigue and displayed a noticeable deterioration in his mental state, likely due to not understanding the underlying cause of his condition. Additionally, he had a history of difficulty in eating and swallowing, along with a significantly dry mouth. Extraoral findings included multiple crusted ulcers on the lower lip, characterized as hemorrhagic bullous lesions, which appeared swollen, cracked, and bled easily. Numerous palpable skin lesions with raised areas, two zones, and marked borders were observed on the skin around the neck, arms, and chest. Upon further examination, these skin lesions were found to occur singly, had a diameter of less than 3 cm, were regularly round-shaped, and had well-defined borders. Importantly, the lesions did not exhibit a positive Nikolsky’s sign. They were fluid-filled rings, paler than the center, consistent with typical target or iris lesions often seen in erythema multiforme, described as atypical, raised targets (Figure 1B). Introraorally, there were multiple bilateral erythematous lesions, mainly on the non-keratinized mucosa, more noticeable anteriorly. Moreover, linear and somewhat symmetrical ulceration on both the right and left sides of the upper and lower vestibule. Additionally, erythema patches associated with ulcerations (tender on palpation) were seen on the buccal mucosa, palate, and labial mucosa, resulting in widespread blistering and ulceration. Some bullae had apparently ruptured, resulting in a hemorrhagic pseudomembranous lip (Figure 1A). Based on the history and lesion presentation, the initial differential diagnosis included drug-induced erythema multiforme (DI-EM), erosive lichen planus, pemphigus vulgaris (PV), pemphigoid (mucous membrane pemphigoid), and paraneoplastic pemphigus (PNP).

Diagnostic tests

After obtaining the patient’s consent, a 3×3 mm incisional biopsy was performed using a 3.0mm diameter sterile single-use biopsy punch. The incisonal biopsy took place at multiple sites on the buccal mucosa (perilesional). The tissue specimen was then sent to the pathology laboratory for Hematoxylin and Eosin-stained tissue sections. Additionally, molecular detection of HSV 1&2 DNA (qualitative) by Real-Time PCR was requested to investigate the presence of Herpes simplex virus (HSV) using a polymerase chain reaction test (real-time PCR employing specific primers and TaqMan probes).
Diagnostic tests result: Histopathology reporting

The presented tissue section showed a superficial stratified squamous epithelium with subtle edema within and between cells and acanthosis of the stratum spinosum (spongiosis was observed). The epithelial tissue exhibited marked vacuolar and hydropic degeneration (Figure 3B). The tissue specimen displayed scattered and diminutive areas of satellite cell necrosis (isolated lymphocyte-encircled eosinophilic necrotic keratinocytes), mainly solo necrotic keratinocytes, with observed Tzank cells (Figure 3C). However, no significant inflammation was noted, except for some perivascular and intraepithelial mononuclear cell infiltration (degree of mononuclear cell infiltration varied), along with minimal eosinophils, neutrophils, basophils, and plasma cell infiltrate (mostly perivascular). No viral cytopathic changes were observed (Figure 3A). The histopathological features of marked vacuolization of the epithelium, intraepithelial and subepithelial separation (acantholytic features), and perivascular and intraepithelial infiltration of mononuclear cells were consistent with immune-vesiculobullous lesions or lichenoid infiltrate.

Real-Time PCR Result

The HSV 1 & 2 by Real-Time PCR were repeated twice and not detected.

Diagnosis

Since the molecular detection of HSV 1&2 DNA was negative, and the patient's genital mucocutaneous tissues were unaffected, it was not indicative of herpes-associated erythema multiforme (HAEM).
While the nasopharyngeal mucosa showed minor involvement and a lack of a positive Nikolsky’s sign, there were face and torso skin lesions and fever. Based on both clinical and histopathological findings, the final diagnosis was established considering the quick onset, rapid recovery, lip involvement, and characteristic target skin lesions. The presented signs and symptoms are consistent with EM, particularly drug-induced EM [1,10].

Management

The first line of action was the immediate discontinuation of the medications that triggered an EM reaction, while addressing the related infections. Despite the lack of evidence, corticosteroids are the most commonly prescribed medications for treating EM. Topical or, when required, systemic corticosteroids are effective in managing EM. The patient was instructed to stop taking antibiotics, and a systemic steroid, prednisolone 20 mg/d, was administered for one week, followed by a tapering dose of 10 mg/d for the second week. Nystatin oral suspension of 4 to 6 milliliters (mL) (about one teaspoonful) four times a day was also prescribed. Healing of the lesions became evident during the third week of follow-up. Analgesic drugs were recommended, and a clear liquid diet was advised.

The first follow-up was one week after the biopsy (the biopsy site was healing well), and there was a noticeable improvement with the medications. The second follow-up was conducted one month later, and the patient experienced complete healing (Figure 2A, 2B). At this stage, the patient was instructed to discontinue the steroid medication and was made aware of the potential for recurrence in the future.

DISCUSSION

DI-EM is rare, and the most common drugs that induce reactions are non-steroidal anti-inflammatory drugs and antibiotics. In this case, the manifestation of the lesion appeared after the intake of initial drugs, which the patient took for 2 weeks. The patient has not been exposed to any kind of infection or previous intake of erythromycin or amoxicillin or allergic to any food additives. The correlation between drug intake and the appearance of the lesion, coupled with the absence of any history of infection and allergy, led to the consideration that the etiological agent was the drugs consumed by the patient. The adverse drug reaction probability by the Naranjo scale was 5.

Differentiating between herpes-associated erythema multiforme (HAEM) and DI-EM was a crucial aspect in achieving a definitive diagnosis. HSV tests were conducted in this case due to a well-established link between HSV infection and EM minor or major, known as HAEM. Several publications have provided evidence that HSV may be the cause of EM. In both the one-time episode and recurring EM, many individuals reported being previously infected with a disease caused by the HSV virus at least two weeks before the condition developed [11,12]. Despite the lack of an apparent clinical connection with an infection caused by HSV [13], the antiviral drug acyclovir is effective in treating a high percentage of individuals suffering from recurring EM [14]. Numerous studies have investigated whether HSV...
or HSV-DNA is present in EM lesions. For instance, Imafuku et al. argued that HSV-DNA is found in 36–81% of the lesions [15]. According to Ng et al., similar percentages of lesions (up to 60%) were positive for HSV-DNA in both single episodes and recurring HAEM (substantiated to be closely linked with an infection caused by HSV), even in EM with no identifiable cause, unrelated to either previous HSV infection or medication intake [16]. These findings suggest that some instances of EM with no identifiable cause may actually be linked to the infection or reactivation of HSV, even though it does not manifest clinically.

Mechanisms causing tissue damage in Erythema Multiforme (EM) vary between viral-associated EM and drug-associated EM, distinct from those observed in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), characterized by extensive damage to epithelial cells with minimal inflammatory infiltration. In drug-associated EM, it is believed that reactive metabolites form through the metabolism of ingested drugs, triggering the disorder. Conversely, in herpes-associated erythema multiforme (HAEM), the tissue damage mechanisms do not appear to result from delayed hypersensitivity reactions. Crucially, T lymphocytes in drug-induced lesions do not release interferon-gamma (IFN-γ), as confirmed by immunocytochemistry staining and in situ hybridization [17]. Instead, drug-associated lesions are characterized by tumor necrosis factor-alpha (TNF-α), expressed in keratinocytes and released by macrophages and monocytes. In contrast, TNF-α has not been identified in HAEM, suggesting a potential lab test for its expression to differentiate HAEM from drug-induced lesions. Due to the absence of an inflammatory response and the role of apoptosis in tissue damage in drug-associated lesions, soluble factors and cytokines have gained recent attention. It has been demonstrated that locally generated TNF-α mediates keratinocyte apoptosis, likely contributing to milder forms of drug-associated EM. Nevertheless, evidence of Fas-FasL interaction exists, particularly in TEN and SJS [18].

Based on its clinical presentation, distinguishing diffuse and widespread oral ulcers from other vesiculobullous diseases like pemphigus or bullous pemphigoid can be challenging. Additionally, toxic epidermal necrolysis (TEN) and herpetic stomatitis should be differentiated from erythema multiforme (EM). The abrupt onset (or recurring nature), periodic eruptions of oral ulcers commonly observed on the lip and mouth anteriorly, pleomorphic dermal sarcoma, and other lesions are more indicative of EM. Since EM diagnosis cannot be established through specific tests, perilesional tissue biopsies and excluding other causes are typically used for di-

**FIGURE 3.** A. A stratified squamous epithelium with marked edema within and between cells, and acanthosis of the stratum spinosum (spongiosis). The epithelial tissue has marked vacuolar and hydropic changes; B. Shows noticeable vacuolization and clefting of the epithelium and the intraepithelial and sub-epithelial separation (acantholytic features), as well as perivascular and intraepithelial infiltration of the mononuclear cells. C. Keratinocytes that are round and large, having basophilic cytoplasm and hyperchromatic nucleus with peri-nuclear halo.
agnostic support. The lesions usually respond to topical steroids, which can be initiated in case of minor lesions, and systemic steroids for severe conditions for a period of one week with a tapering dose. In this patient, the offending drugs were discontinued, and systemic steroids were prescribed for a week and later tapered. The lesions healed completely in 10 days without any scar formation.

**CONCLUSION**

DI-EM is diagnosed by excluding other conditions associated with chronic inflammation or the formation of vesicles or bullae and myelodysplastic syndrome. The diagnosis requires a thorough patient history and clinical examination to rule out other chronic mucocutaneous disorders, including pemphigus, PNP, MMP, and OLP. In order to rule out any further EM variant or other disease entities, a biopsy specimen must be examined using standard histopathological and immunopathological techniques. Cessations of causative drugs and supportive medications can result is complete resolution of the conditions, hence early diagnosis plays a key role in managing the condition.

**Data availability:** data supporting this research article are available from the corresponding author or first author on request

**Consent:** the patient’s written consent was obtained

**Conflict of interest:** the authors declare no conflicts of interest

**Financial support:** none declared

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**REFERENCES**