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Original Article

METHOTREXATE-INDUCED ORAL ERYTHEMA MULTIFORME

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ABSTRACT

Objective: To discuss the management of oral erythema multiforme (EM) due to methotrexate (MTX) in gestational trophoblastic tumor patients.

Methods: A 28-year-old woman was referred to the Oral Medicine Clinic with complaints of pain throughout the oral cavity accompanied by blackish encrustation on the upper and lower lip for 5 d. She previously underwent the first cycle of chemotherapy using MTX for the treatment of a gestational trophoblastic tumor. Extraoral, multiple diffuse blackish patches on the face and haemorrhagic crusts on the lips with painful erosions. Intraoral, multiple erosive and ulcerative lesions on the labial and buccal mucosa.

Results: Management involved topical 0.025% hyaluronic acid mouthwash for erosion and ulceration, compressed 0.9% NaCl for crusted lesions on the lips, and petroleum jelly for the non-crusted lesions on the lips. Complete healing of oral and lip lesions was achieved within 10 d.

Conclusion: Pharmacological management should be tailored to each patient with careful consideration of treatment risk or benefit. In our case, the use of non-steroidal anti-inflammatory topical agents was considered successful in treating oral EM.

Keywords: Oral erythema multiforme, Adverse drug reaction, Ulceration, Saline, Hyaluronic acid

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INTRODUCTION

Adverse drug reactions (ADRs) have different clinical patterns, such as erythema multiform (EM), Steven-Johnsons syndrome (SJS), anaphylactic stomatitis, intraoral fixed drug eruptions, lichenoid drug reactions, and pemphigoid-like drug reactions [1]. Erythema multiforme (EM) is a self-limited, acute mucocutaneous inflammatory disease that affects the skin and mucosa [2]. The term erythema multiforme was first introduced by Ferdinand von Herbra in 1860. He stated that patients with EM had at least the acrally distributed typical target lesions or raised oedematous skin papules, with or without mucosal involvement [3]. Then in 1968, Kenneth reported 9 cases of EM at East Man Dental Hospital and described an inflammatory disorder of the oral cavity with typical lesions affecting the lips, cheeks, and tongue but without skin involvement [4].

Oral EM is classified as the third category, apart from EM minor and EM major. The patient has a clinical picture of lip and oral ulceration like typical EM but without target lesions on the skin. The oral mucosa is the primary location for EM. However, it can become more severe with skin involvement if subsequent exposure is not treated appropriately. Therefore, identifying and differentiating EM lesions from other ulcerative disorders in the oral cavity is important to provide prompt management and appropriate follow-up [4]. The pathogenesis of EM is not well established, but it is related to immune-mediated disorders. The etiology of EM is divided into two main categories: infections and drugs. Compared with drugs, 90% of EM cases are more often caused by infections, including herpes simplex virus infections (HSV 1 and HSV 2), Mycoplasma pneumonia, Eipstein-Barr virus, and fungi. Meanwhile, drug etiologies consist of antibiotics (penicillins, tetracyclines, and cephalosporins), macrolides, sulphonamides, anti-tuberculosis agents, antipyretics, non-steroidal anti-inflammatory drugs, antiepileptic agents, barbiturates, phenothiazines, statins, tumor necrosis-α factor inhibitors, and vaccines [2, 5]. This article aimed to discuss the management of oral EM caused by methotrexate as a chemotherapeutic agent for gestational trophoblastic tumors. The lesion was treated with non-steroidal anti-inflammatory topical agents to relieve the symptoms.

MATERIALS AND METHODS

A 29 y old woman was referred to the Department of Oral Medicine, Dr. Hasan Sadikin General Hospital, with complaints of pain throughout the oral cavity and difficulty in swallowing for the past 5 d. She could only consume milk given to her by the hospital. The first complaint appeared after undergoing chemotherapy on the second day of the first cycle (medication given was methotrexate 300 mg/m^2). Her symptoms started with a burning sensation, followed by the appearance of black patches all over the face and body, accompanied by swelling of the lips. She had no previous history of recurrent ulceration and complaints of blisters on other body parts. The history of fever after drug intake was denied. The previous history of food or drug allergy was denied.

The diagnosis from the Department of Obstetrics and Gynecology was stage 1 gestational trophoblastic tumor, and from the Department of Dermato-Veneorology was toxicity rash due to methotrexate (MTX). During the hospitalization, the therapy provided were 10% urea lotion, 1 mg folic acid, and 10 mg cetirizine. Laboratory examination results showed a decrease in hemoglobin levels (7.0 g/dl), erythrocytes (2.88 million/µl), hematocrit (20.9%), leukocytes (2.41x10^3/µl), platelets (14,000/µl), mean corpuscular hemoglobin (MCH; 24.3 pg), mean corpuscular volume (MCV; 72.6 fL), rod neutrophils (2%), total lymphocytes (0.77x10^3/µl), total neutrophils (1.21x103/µl), total basophils (0.00x103/µl) and an increase in the number of eosinophils (5%), monocytes (13%), SGOT (45U/l) (table 1).

On extraoral examination, diffuse blackish brown patches almost all over the face to the neck (fig. 1A), and blackish hemorrhagic crusts accompanied by erosion, oval in shape, ±7 mm in diameter, irregular border, painful, and without tendency to bleed on touch on the upper and lower lips (fig. 1B). No target lesion was found on the skin surface of her body or extremities. On intraoral examination, multiple erosions, ±5-8 mm in diameter in the upper and lower labial mucosa as well as the right and left buccal mucosa near the corners of the lips (fig. 1 C-F). The mouth opening was reduced because of marked tenderness around ulceration.

RESULTS

Based on the history and clinical findings, the provisional diagnosis was drug-induced erythema multiform (DIEM) et causa methotrexate. Informed consent regarding the patient's photograph and the publication had been obtained from the patient. The non-pharmacological treatments were oral hygiene instruction (OHI) and education to the patient. The pharmacological treatment includes

compressing the lips with gauze soaked in 0.9% NaCl solution for 5-15 min, 4-5 times a day; cleaning the teeth and tongue using gauze soaked in 0.9% NaCl 2 times a day; mouth-rinsing using 10 ml of 0.025% hyaluronic acid solution 3 times a day; compressing erosive lesion on the lower lip using gauze soaked in 0.025% hyaluronic acid solution; and applying a thin layer of petroleum jelly on the upper and lower lip area with no erosive lesion, at least 3 times a day. She was instructed to avoid hard, spicy, hot, and sour foods, as well as consulted to check IgE levels, erythrocyte sedimentation rate (ESR), and c-reactive protein (CRP). One day later, the results showed an increase in IgE levels (248.3 IU/ml), ESR (83 mm/hour), and C-reactive protein quantitative (CRP = 4.92 mg/dl) (table 1).

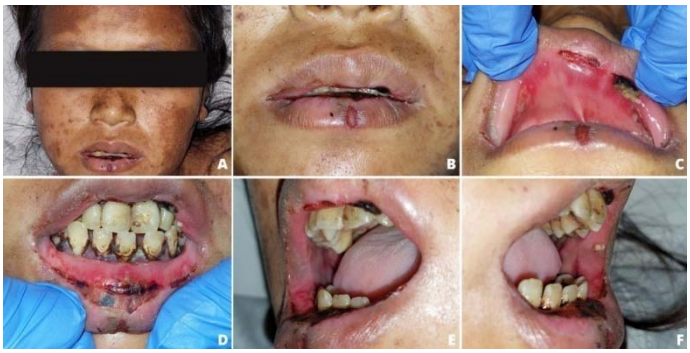

Fig. 1: Patient condition on day 1. (A) Blackish brown patches on almost all parts of the face and neck, (B) Erosion and black haemorrhagic crusts on the lips, (C, D) Ulceration and erosion of the upper and lower labial mucosa, (E, F) Ulceration and erosion on the left and right buccal mucosa

Table 1: Laboratory Investigation results

Laboratory parameter	Results	Normal value	Unit
Hemoglobin	7.0*	12.3–15.3	g/dl
Hematocrit	20.9*	36.0–45.0	%
Erythrocyte	2.88*	4.5–5.1	million/µl
Leukocytes	2.41*	4.4–11.3	10^3/µl
Platelets	14*	150–450	10^3/µl
MCV	72.6*	80–96	fL
MCH	24.3*	27.5–33.2	Pg
MCHC	33.5	33.4–35.5	%
Eosinophils	5*	0–4	%
Stem neutrophils	2*	3–5	%
Erythrocyte Sedimentation Rate (ESR)	83*	<20	mm/h
Quantitative CRP	4.92*	<0.3	mg/dl
IgE	248.3*	<100	IU/ml

Abbreviations: Abnormal value was indicated with (*); MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; pg, picograms; fL, femtoliter.

On the 5th day after therapy, complaints had improved. She was able to consume solid food. On extraoral examination, diffuse blackish-brown patches were almost all over the face (fig. 2A), and encrustation as well as erosion on the lower lip, had improved (fig. 2B). On intraoral examination, the lesion on the upper labial and buccal mucosa had improved (fig. 2 C, E, F). The lower labial mucosa showed diffuse erythematous macules near the border of the lips and labial mucosa (2D). She was advised to continue the therapy given before.

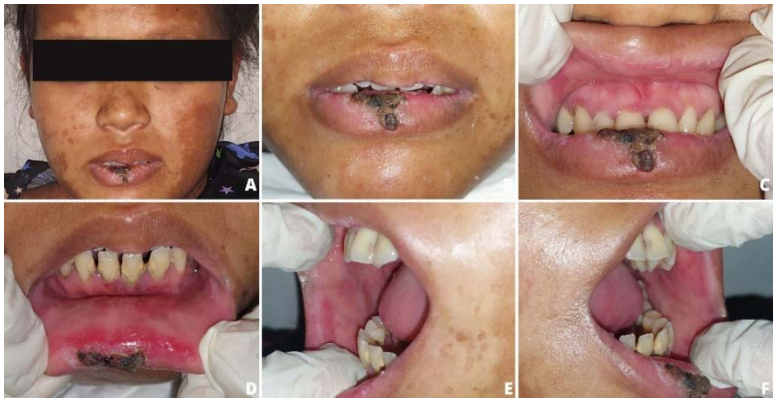

Fig. 2: Patient condition on day 5. (A) Blackish brown patches on almost all parts of the face and neck, (B) Erosion and black hemorrhagic crusts on the lips, (C) Lesion on the upper labial mucosa had improved, (D) Diffuse erythematous area on the lower labial mucosa, (E, F) Lesion on the left and right buccal mucosa had improved

On the 10th day after therapy, complaints had improved. Extraoral encrustation on the lower lip had improved (fig. 3A, B). Intraoral, ulceration, and erosion had improved (fig. 3 C-F). She was advised to maintain oral hygiene, continue to apply petroleum jelly to the upper and lower lips, and maintain a healthy and balanced lifestyle.

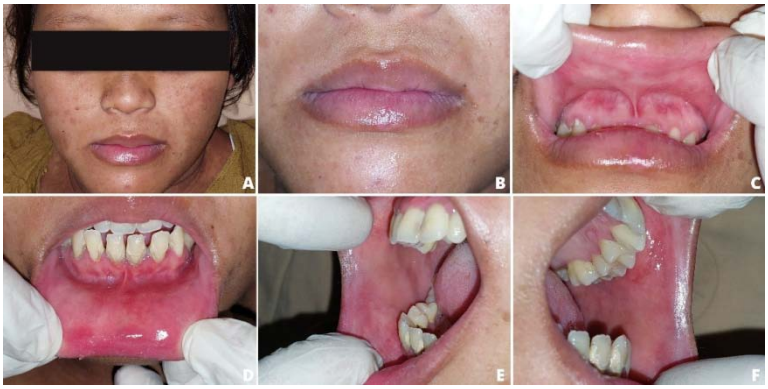

Fig. 3: Patient condition on day 10. A) Blackish-encrustation on the lower lip improved. B) Upper labial mucosa showed improvement. C) The lower labial mucosa still has areas of diffuse erythema. D, E) Right and left buccal mucosas showing improvement

DISCUSSION

Drugs are like double-edged swords. On the one hand, they can provide benefits, but on the other hand, they can cause unwanted reactions known as adverse drug reactions (ADRs). ADR is an unpleasant or quite dangerous reaction due to medication. It predicts the possible harm of subsequent administration, allows for prevention, a change in dosage regimen, or even discontinuation of the product [6]. For decades, ADRs have been classified into type A and type B reactions. Type A reactions are associated with excessive pharmacological action of the drug (augmentation) when administered in recommended therapeutic doses. Type A reactions are usually dose-dependent, predictable, easy to recognize, and reversible with dose reduction or drug discontinuation. In contrast, type B reactions are pharmacological reactions to drugs that are idiosyncratic, rare, or novel responses and cannot be predicted. It occurs less frequently than type A reactions, accounting for a total of around 20% of all ADR cases, for example, anaphylactic responses due to the use of penicillin and chloramphenicol-induced aplastic anemia [7]. Some drugs associated with ADR-related hospitalization include antiplatelets, anticoagulants, cytotoxic agents, immunosuppressants, diuretics, antidiabetics, and antibiotics [6]. In the oral cavity, ADR has a diverse clinical presentation, including oral ulceration, mucositis, and erythema multiform (EM) [8].

EM is a cutaneous and mucosal hypersensitivity reaction with characteristic lesions that are triggered by a specific antigenic stimulus. It is an acute, sometimes recurrent condition of the skin and mucous membranes with papular, bullous, and necrotic lesions. Most lesions appear after 48 to 72 h and are more commonly found on the extremities. The lesions are usually localized on one side and heal within 7 to 21 d [9]. EM is a disease that reacts mainly to antigens produced from exposure to microbes and medications. Its attacks can be precipitated by preceding HSV infection, especially herpes labialis, which is reported in 71% of all EM cases and the use of some medications and is classified as a rare case with a prevalence of less than 10%. EM caused by HSV infection is known as herpes-associated erythema multiform (HAEM), whereas EM caused by medications is known as drug-induced erythema multiform (DIEM) [8, 9].

DIEM differs mechanically from HAEM. DIEM involves the expression of tumor necrosis factor-α (TNF-α), whereas herpes-associated erythema multiform (HAEM) involves interferon-γ. In DIEM, the disease process often involves the abnormal metabolism of the causative drug [10]. This is characterized by changes in drug metabolism leading to the cytochrome p450 metabolite pathway, which results in the production of reactive and toxic metabolites. The main tissue damage that occurs is not due to the inflammatory response but rather by apoptosis [8]. Causative drugs include non-steroidal anti-inflammatory drugs (NSAIDs), β-lactam antibiotics (such as penicillins and cephalosporins), non-β-lactam antibiotics (such as clindamycin and trimethoprim), macrolides, anticonvulsants (carbamazepine, phenytoin).), barbiturates, oral antidiabetics (such as sulphonamides, chlorpropamide, tolbutamide), codeine, furosemide, anti-tuberculosis agents, antipyretics, gold, and protease inhibitors [11]. In one study, it was stated that 2.06% of cases of EM were caused by diclofenac sodium, 6.17% of cases were due to paracetamol, 5.65% were due to anti-tubercular drugs, 5.39% were due to penicillins, 3.34% were due to antiretrovirals and 3.08% were due to cephalosporins [12]. To the best of the authors' knowledge, to date, there are few in the literature reporting on EM, particularly oral EM, resulting from the use of intravenous MTX as a chemotherapeutic agent for gestational trophoblastic tumors.

Methotrexate (MTX) is a folate analog and a chemotherapeutic agent for treating various types of cancer [13]. It acts by inhibiting dihydrofolate reductase due to polyglutamate accumulation, thereby preventing the synthesis of purines, pyrimidines, polyamines, and the transmethylation of other compounds. Purines and pyrimidines are precursors to DNA and RNA. At high doses, it prevents cell proliferation by preventing the production of DNA and RNA, making it effective for the treatment of malignancy. The cessation of purine synthesis can cause the cessation of the cell cycle in the S phase [14]. It is used at low doses (<50 mg/m^2), moderate doses (50–500 mg/m^2), and high doses (>500 mg/m^2). High-dose MTX is used for central nervous system (CNS) prophylaxis in acute lymphoblastic leukemia and lymphoma. High-dose MTX is also frequently administered in the treatment of primary CNS lymphoma, leptomeningeal metastases, and osteosarcoma. Moderate and low-dose MTX is used for gestational trophoblastic diseases and inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, hidradenitis suppurative, and graft versus host disease [15].

It is often used as first-line therapy for gestational trophoblastic tumor with commonly used routes of administration including intramuscular (IM), intravenous (IV), and some are given orally [16]. ADR due to MTX were found in various ways of administration, including low doses, high doses, oral, and intrathecal. The disease mechanism is not fully understood [17, 18]. These are divided into three main groups. The first group includes direct gastrointestinal and bone marrow toxicities. Both are dose-dependent, although the relationship between plasma concentrations and the effect is not fully understood. These effects are mediated by folate antagonism and are the most common. The second group includes idiosyncratic or allergic reactions such as pneumonitis. The third group includes long-term effects of treatment, such as liver or cardiovascular disease, caused primarily by hyperhomocysteinemia. The most common adverse reactions found include gastrointestinal toxicity

(i.e. nausea, vomiting, indigestion, anorexia, dyspepsia, diarrhea, malaise), hepatotoxicity (i.e. hepatitis, fibrosis, cirrhosis), myelosuppression (i.e. leukocytopenia, thrombocytopenia, pancytopenia), hyperhomocysteinemia, hypersensitivity causing toxicity pulmonary, renal insufficiency, central nervous system disorders (i.e. headaches, depression), and osteoporosis. Oral lesions in ADR due to MTX are generally associated with drug overdose or folate deficiency [19]. These oral lesions include ulcerative stomatitis, mucositis, and at high doses, can cause EM [18].

Aside from EM, another MTX adverse effect that should be taken into consideration is oral mucositis. Oral mucositis is the most frequent finding among dentists and is usually dose-dependent. It is an inflammatory lesion of the mucosa resulting from chemotherapy or, radiation therapy or chemo-radiation therapy. It occurs in 40% of patients undergoing chemotherapy [20]. The incidence of oral mucositis varies for each chemotherapeutic agent, especially those that affect DNA synthesis (S-phase), such as 5-fluorouracil, methotrexate, and cytarabine [21]. The predisposition to most MTX adverse reactions includes factors such as folate deficiency and continued use of other anti-folate drugs [22]. Chemotherapy-induced mucositis usually develops within 5 to 14 d of therapy, before the onset of pancytopenia, because an accumulation of MTX is higher in mucosal epithelial cells than in bone marrow stem cells [23]. Oral mucositis starts with mucosal erythema, which then develops into erosions and ulcerations. Ulcer locations are generally limited to non-keratinized surfaces in the oral cavity, such as the buccal mucosa, lateral tongue, ventral tongue, and soft palate [21].

Based on these descriptions, the diagnosis was drug-induced oral EM caused by MTX, although the lesions were confined to the lips and oral mucosa without target lesions on the skin. Oral EM is a rare variant with clinical appearances ranging from superficial erythema and hyperkeratotic plaques to very painful erosions and deep hemorrhagic bullae. The bullae rupture very easily, resulting in erosion of the oral cavity with clear boundaries and crusted lesions on the lips. These lesions are sometimes difficult to differentiate from other vesicobullous and ulcerative disorders that have a similar clinical presentation. Among the oral mucosa, the most frequently affected areas are the labial mucosa, buccal mucosa, lips, and followed by the palatal mucosa [11]. In contrast, oral mucositis is more common in the buccal mucosa, lateral tongue, ventral of the tongue, soft palate and is not accompanied by hemorrhagic crusts on the lips.

Management of EM depends on the presence or absence of mucosal manifestations, the disease recurrences, and the overall severity of the disease. To date, there has been no specific treatment for EM. Eliminating all precipitating factors is an important component of the treatment of EM cases; thus, the first course of action in cases of EM caused by drugs is to discontinue the drug and avoid successive re-exposure to the same drug or exposure to drugs with the potential for cross-reactivation with similar chemical structures [24]. Corticosteroids are the most commonly used drugs, although there is little evidence for their use in treating EM. The use of corticosteroids, unfortunately, can give rise to some side effects. In general, the treatment of mild EM focuses on symptom relief using topical anti-inflammatory agents, anesthetics, or pain relievers. EM is severe; generally, the lesions are more extensive, or the lesions can impair food intake. Mild oral EM can be treated with topical or systemic analgesics for pain relief, topical antiseptics, and supportive therapy because the disease is self-limiting and resolves within a few weeks. Meanwhile, more severe cases can be treated with systemic corticosteroids [9, 25, 26].

Management of this patient includes administering non-steroidal anti-inflammatory mouthwash containing 0.025% hyaluronic acid, 0.9% NaCl compressed on lips with erosion and hemorrhagic crusts, and application of petroleum jelly on the non-crusted parts of the lips. The administration of 0.25% hyaluronic acid is intended to treat erosion and ulceration of the oral mucosa. Hyaluronic acid mouthwash for oral ulceration was chosen because of its good safety and efficacy compared with other anti-inflammatory drugs, such as corticosteroid mouthwash [27]. Hyaluronic acid (HA) plays an important role in various biological processes, such as cell signaling, morphogenesis, matrix formation, tissue hydration, lubrication, wound healing, gene expression regulation, and cell proliferation [28]. It coats the oral mucosa, enhances tissue hydration, and accelerates healing [29]. Regardless of the stage of ulceration, it can relieve pain more quickly compared to corticosteroid ointments and has a lower risk of complications, discomfort, and drug interactions. In addition, there is no risk of overdose with HA, and it is safer than corticosteroids if given to younger patients (for example, children or toddlers), patients who have difficulty following instructions, and pregnant women. It is also available in many countries [27, 30].

She was instructed to routinely compress her lips using gauze soaked in 0.9% NaCl on the lips. 0.9% NaCl is an isotonic liquid generally used for wound cleansing and compatible with human body tissues. 0.9% NaCl can moisturize the lips, prevent water evaporation, accelerate healing, not cause allergies or sensitization, not damage tissues, and not affect the function of fibroblasts and keratinocytes in wound healing. The resulting moist conditions can assist in the processes of healing, growth, division, and cell migration to enhance the formation of new tissue by preventing dehydration, increasing angiogenesis and collagen synthesis, and increasing the breakdown of dead tissue and fibrin [31-33].

In addition, applying 0.9% NaCl compressed to the lesion can reduce oedema since saline can attract fluid from the lesion through osmosis. It has an anti-inflammatory response; hence it can reduce symptoms of pain and erythema from lesions, as well as increase blood flow to the lesion and fasten the healing process of the lesion [34]. On the lips that are not crusted, she was instructed to apply a thin layer of petroleum jelly regularly. This aims to keep the condition of the non-crusted lips moist to reduce discomfort to the patient. White petroleum jelly, also known as vaseline album or white petrolatum, is a mixture of mineral oil, paraffin, and microcrystalline wax [35, 36]. It has been used since 1872 as a moisturizer consisting of long-chain aliphatic hydrocarbons. The petroleum jelly cream will melt into the outer part of the skin, entering the spaces between cells and gaps in the lipids. It can reduce transepidermal water loss to make body parts naturally moisturized [37], protects them from external irritation and secondary infection to accelerate the healing process [37, 38].

The pain and ulceration in the patient's oral cavity had improved after 3 d of administering non-steroidal anti-inflammatory mouthwash containing 0.025% hyaluronic acid, thus the patient was able to consume solid foods. Erythematous patches improved completely on the 10th day of therapy. The crusts on the lips peeled off on the 6th day of therapy and the erythematous patches improved on the 10th day.

CONCLUSION

Oral EM due to MTX is considered less reported. It is an incapacitating disease, thus providing therapy for the patient must consider the general condition of the patient, and the risks and benefits of the treatment given. Management of the lesions in the oral cavity can be done by administering non-steroidal anti-inflammatory mouthwash such as 0.025% hyaluronic acid, compressing gauze soaked in 0.9% NaCl, applying petroleum jelly, and maintaining oral hygiene to prevent secondary infections.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interest in this article.

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