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 hemorrhagic 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

INTRODUCTION

Adverse drug reactions (ADRs) have different clinical patterns, such as erythema multiforme (EM), Steven-Johnson syndrome (SJS), anaphylactic shock, 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 Herber 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 herps simplex virus infections (HSV 1 and HSV 2), Mycoplasma pneumoniae, Epstein-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-alpha 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/m2). 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/ml saline, and 1 mg/ml hyaluronic acid. Laboratory examination results showed a decrease in hemoglobin levels (7.0 g/dl), leucocytes (3,000/mm3), hematocrit (20.9%), leucocytes (2.41x103/mm3), platelets (14,000/mm3), mean corpuscular hemoglobin (MCH; 24.3 pg), mean corpuscular volume (MCV; 72.6 fl), red neutrophils (0.07x109/mm3), total lymphocytes (0.77x109/mm3), mean total neutrophils (1.21x109/mm3), total basophils (0.00x109/mm3) and an increase in the number of eosinophils (5%), monocytes (13%), SGT (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, ± 8 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. On intraoral examination, multiple erosions were crater-shaped, ± 5-8 mm in diameter in the upper and lower lips (fig. 1B). No target lesion was found on the skin. The mouth opening was reduced by half because of marked tenderness around ulceration.

RESULTS

Based on the history and clinical findings, the provisional diagnosis was drug-induced erythema multiforme (DEM) 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).

![Patient condition on day 1](image1)

**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>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Results</th>
<th>Normal value</th>
<th>Unit</th>
</tr>
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<tbody>
<tr>
<td>Hemoglobin</td>
<td>7.0*</td>
<td>12.3–15.3</td>
<td>g/dl</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>20.9*</td>
<td>36.0–45.0</td>
<td>%</td>
</tr>
<tr>
<td>Erythrocyte</td>
<td>2.88*</td>
<td>4.5–5.1</td>
<td>million/μl</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>2.41*</td>
<td>4.4–11.3</td>
<td>10³/μl</td>
</tr>
<tr>
<td>Platelets</td>
<td>14*</td>
<td>150–450</td>
<td>10³/μl</td>
</tr>
<tr>
<td>MCV</td>
<td>72.6*</td>
<td>80–96</td>
<td>fl</td>
</tr>
<tr>
<td>MCH</td>
<td>24.3*</td>
<td>27.5–33.2</td>
<td>Pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>33.5</td>
<td>33.4–35.5</td>
<td>%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>5*</td>
<td>0–4</td>
<td>%</td>
</tr>
<tr>
<td>Stem neutrophils</td>
<td>2*</td>
<td>3–5</td>
<td>%</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate (ESR)</td>
<td>83*</td>
<td>&lt;20</td>
<td>mm/h</td>
</tr>
<tr>
<td>Quantitative CRP</td>
<td>4.92*</td>
<td>&lt;0.3</td>
<td>mg/dl</td>
</tr>
<tr>
<td>IgE</td>
<td>248.3*</td>
<td>&lt;100</td>
<td>IU/ml</td>
</tr>
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</table>

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.

![Patient condition on day 5](image2)

**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 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 pemphigus. 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.
in ADR due to MTX are generally associated with drug overdose or 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 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. While 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 lips. 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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CONFLICT OF INTERESTS

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