Cotrimoxazole Induced Erythema Multiforme: A Case Report
Aman Chowdhry, Ankita Tandon

Abstract
Erythema Multiforme is an acute inflammatory disease of the skin, considered to be hypersensitivity reaction to infection and drugs. Sulfa drugs are the most common triggers considered. Here is the case of Erythema multiforme secondary to drug reaction from cotrimoxazole. Patient had oral and skin manifestations and was treated with systemic corticosteroids. No complications were seen on further follow-up.

Keywords: Cotrimoxazole; Encrustations; Erythema Multiforme; Naranjo Algorithm; Sulfa drug; Target lesions.

Introduction
Erythema multiforme (EM) is an acute, intermittently recurring hypersensitivity condition of the skin and mucous membranes described by Hebra in 1866.1,2 EM typically affects young adults of age group between 20 to 40 years and about 20% of cases occur in children. EM with mucosal involvement is called erythema multiforme major; in the absence of mucosal disease, EM is called erythema multiforme minor.3 EM is considered to be associated with certain infections and medications.4,5 The most common offending drugs consist of sulfonamides, non-steroidal anti-inflammatory drugs, antituberculous drugs, antibiotics, pyrazolones, phenylbutazone and antiepileptic drugs (AEDs).6 Sulfa drugs are the most frequent triggers.7 Cotrimoxazole is a sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole. It is used in the treatment of a variety of bacterial infections and its adverse effects comprise cutaneous hypersensitivity reactions including EM.8 Here is a case of EM involving oral cavity and skin in a 37 year old female which developed secondary to the intake of cotrimoxazole.

Case Report
A 37 year old female patient (weighing 51 kg) visited dental clinic with complaints of painful oral ulcers, hemorrhagic crusts on the lips and febrile episodes since past four days. Patient also reported of conjunctival soreness, odynophagia and dysarthria since two days. History revealed that, patient was being treated for urinary tract infection with cotrimoxazole. The presentation of the patient strongly correlated with intake of cotrimoxazole, as the signs and symptoms have started appearing four days after intake of cotrimoxazole. Also, patient had never experienced similar lesions in the past. On clinical examination, lower lip had deep red to dark brown encrustations with erythematous borders (Fig 1a). No cervical nodes were palpable. A diagnostically significant finding was the presence of characteristic target lesions on the extremities (Fig 1b & 1c). On intra oral examination the entire oral cavity appeared blanched. The tongue was appearing grayish black in color (Fig 1d).

The patient family history was non contributory. The complete hemogram revealed that patient was anemic (8.0 gm%). ESR was raised (Westergreen method); random blood sugar level was 150 mg%. Investigations for hepatitis B and C, and HIV (Tridot test) were negative. Cotrimoxazole therapy was stopped immediately and the patient was prescribed with tab. Prednisone 20 mg twice daily and tabs Paracetamol 500 mg thrice daily for a week. Ointment 0.1% Triamcinolone Acetonide was prescribed for topical application. Mouthwashes consisting of local anesthetics and antiseptics were added for symptomatic treatment. As suggested by Habif TP9 steroid dose was tapered after a week and patient was recalled. After 15 days of medication there was complete resolution of swelling and crustations on the lips. The patient was kept on surveillance for 2 months; in this interlude there was no recurrence. Naranjo algorithm, Naranjo Scale, or Naranjo Nomogram (Table 1) explains and scales the adverse drug reaction associated with drugs.10 In this case Naranjo score is seven in association with drug cotrimoxazole.
Discussion
Erythema multiforme is an acute inflammatory disease of the skin and mucous membrane that causes a variety of skin lesions. The differential diagnosis of early onset erythema multiforme includes drug eruption, polymorphic light eruption, urticaria, urticarial vasculitis, viral exanthems and other hypersensitivity reactions.12

Figure 1: The clinical photographs of the patient showing Lower lip having deep red to dark brown encrustations with erythematous borders (a), Target lesion on ventral aspect of right foot (b) and on left hand (healing) between thumb and index finger (c), and Blanched oral cavity & grayish black discoloration of tongue (d).

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
</tr>
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<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2. Did the adverse event appear the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
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<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>4. Did the adverse reaction reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
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<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
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<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
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<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
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<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
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Total Score

Table 1: Naranjo algorithm, Naranjo Scale or Naranjo Nomogram. The total score calculated from this table defines the category of an adverse reaction. The categories are defined as follows: Definite (Certain) (total score>8); Probable (total score 5-8); Possible (total score1-4); Doubtful (Unlikely) (total score<1).

The exact pathogenesis of EM is unknown. EM is an immunological reaction to a drug or various infections, notably herpes simplex virus (HSV). Herpes induced EM is most
likely cell-mediated immunity against virus and begins with the transfer of Simplex Virus (HSV)- Deoxyribonucleic acid (DNA) fragments by circulating peripheral blood mononuclear CD3+ cells (Langerhans cell precursors) to keratinocytes, which is followed by recruitment of HSV-unique CD4+ TH1 cells. CD4+ cells release interferon-γ (IFN-γ) in response to virus associated antigens, this initiates inflammatory cascade and immunomeditated epidermal damage subsequently begins.\(^3\)\(^{-}\)\(^{17}\)

In contrast, drug induced EM appears to involve CD8+ T-cell attack and expresses tumor necrosis factor alpha (TNFα) in affected epithelium in the absence of HSV-DNA.\(^1\)\(^{8}\)

Our case was typical example of drug induced EM as patient gave history of rashes on skin and oral lesions started after taking medication. Characteristic encrustations and bleeding from the lips was present. The diagnosis was made on the basis of the total clinical picture, including the rapid onset of lesions, mucous membrane involvement and target (iris) lesions. The viral lesions (especially primary herpes simplex infection) were ruled out as they lesions would be small, round, symmetric, and shallow\(^1\)\(^{11}\) where as our case presented larger, irregular, deeper, bleeding lesions with prominent involvement of lips. Since viral infection was ruled out as a triggering agent and the culprit was adverse drug reaction and the drug was immediately stopped. Patient responded to systemic corticosteroids and no complications were seen.

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