Case Report:
A Case of Erythema Multiforme Caused by Sildenafil Plus Tramadol

Amir Hossein Ghanbarzamani[1*], Ebrahim Salehifar[1], Kaveh Kazemian[2]

1. Pharmaceutical Research Center, Department of Clinical Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
2. Department of Clinical Pharmacy, Sina Hospital, Tehran University of Medicine, Tehran, Iran.

*** Corresponding Author:**
Amir Hossein Ghanbar Zamani, PharmD.
Address: Pharmaceutical Research Center, Department of Clinical pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
Phone: +98 (21) 44069924
E-mail: amirh.ghzamani@gmail.com

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ABSTRACT

In this report, we present a 29-year-old man who experienced EM five days after using sildenafil and tramadol. Based on clinical examination and history, the diagnosis of EM was made confirmed via skin biopsy, which found intra-epidermal bulla filled by fibrinous exudate, some mononuclear cells, and a few eosinophils. The spongiotic epidermis showed lichenoid interface dermatitis, eosinophilic spongiosis, and necrolysis, consistent with EM diagnosis. Fluocinolone, 0.025% ointment, was prescribed for the patient, and the lesions healed after two weeks of treatment.

Introduction

Erythema Multiforme (EM) is an acute eruption caused by infection and drug allergies. This is a type IV allergic reaction manifested with varying severity. Viral (the most common type is Herpes Simplex Virus; HSV), bacterial and fungal infections can cause this reaction too [1, 2].

EM has recently been identified as a different disease from Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Because of the acute course of the disease and the lack of a universally accepted classification system in this regard, epidemiological data on EM are limited. Current data show that its prevalence is <1% and is higher in women between the ages of 20 and 40 years [3].

EM initially appears with several distinct red and sharp pink macules that may later transform into large plaques. Target lesions may occur a few days after disease onset. The lesions have a darker central red area, a bright pink area, and an environmental red ring [3, 4].

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No specific histopathological pathognomonic features for EM have been described. Because laboratory tests are non-specific, the diagnosis and management should be conducted based on the patient's history, clinical results, and imaging. The first step in the management of EM is to identify the cause of EM (such as drug or suspected infection). Mild EM cases do not require treatment, although some topical steroids or oral antihistamines may be used. If the cause is HSV, the oral form of acyclovir should be used because the topical form may not have a therapeutic effect [3, 4].

Case Report

A 29-year-old man was referred to an allergy clinic at Sina Hospital in Tehran, Iran, for mild itching and erythema. The lesions were limited to the hands and feet and had started about 12 hours before presentation. No other symptoms were reported, and no abnormalities were seen on physical examination. The next morning, he woke up with severe itching and noticed a sizeable maculopapular rash on his hands and feet. He was then re-examined. In addition to the scattered injuries mentioned above, a single target was found on his left leg. No other sites, such as oral mucosal lesions or epidermal or blister separation, were involved.

A diagnosis of EM was made. Blood samples were obtained to assess the patient's biochemical status, and a skin biopsy was ordered. On drug history, it was found that the patient took sildenafil (100 mg) and tramadol (50 mg) three times five days before the initial visit. He recalled that a year ago, he once again used sildenafil 100 mg plus tramadol 50 mg. Because HSV is a common cause of EM, the history of HSV was recorded, and he was examined regarding the HSV lesions, but the results were negative. Fluocinolone (0.025%) ointment twice daily was prescribed, and he was asked to report an increase in the number of lesions. Laboratory tests were within the normal range (Table 1).

Skin biopsy findings consisted of intra-epidermal bulla filled by fibrinous exudate, some mononuclear cells, and a few eosinophils. The spongiotic epidermis showed lichenoid interface dermatitis, eosinophilic spongiosis, and necrolysis, consistent with a diagnosis of EM. He was re-examined 3 days later. The severity of itching had decreased, and very mild itching was present. The process of skin healing was evident, and the lesions entirely healed after two weeks.

Discussion

In this report, we present a rare case of EM following sildenafil and tramadol use. As we know, only a few case reports of sildenafil-associated EM have been reported, and only one report of EM following tramadol use could found [5]. One of the outstanding features of EM is the targetoid lesions located at the level of the limb extensor. These lesions may be major or minor. Conflicts can be in the neck, palms, trunk, and flexor surface. The lesion has a central blister surrounded by a red, inflamed area and an erythematous halo. EM can also cause mucosal involvement in the mouth, eyes, and genitals [6-9].

The lesions appear within 3 to 5 days and resolve within 2 to 3 weeks; however, in severe cases, this may take 6 weeks. These lesions may appear 6 times a year or stay with the patient for 6 to 10 years. In rare cases, a persistent appearance of uninterrupted lesions caused by a virus can last for up to one year. In some cases, corticosteroid intervention can reduce patients' symptoms, although the clinical course of EM is self-limited [8, 10].

In the past, EM was thought to be part of the Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), but studies show that EM is a distinct disease and should not be confused with SJS/TEN. Because of the different causes and prognosis of the lesions, precise diagnosis and specific management of each condition are important [8, 11].

Severe Cutaneous Adverse Reactions (SCAR) of drugs refers to relatively rare events with presentations such as SJS and TEN. These events are associated with high mortality rates and severe complications. A case study of multinationals conducted in Europe in 1997 and 2001 shows, in about 100 million people who entered the study, 379 patients showed SCAR [12-14].

As noted, there are very few case reports of EM following sildenafil. For instance, a 49-year-old man who was HIV-positive showed EM symptoms 5 days after taking sildenafil [3].

As our patient used tramadol in addition to sildenafil, it may be proposed that tramadol may increase the risk of EM in patients receiving both drugs concurrently, but this theory needs more clinical evidence. Considering misuse and abuse of both sildenafil and tramadol [6], we have reported this case to highlight the unusual drug-related cause of EM. The possible mechanism for these drugs can be attributed to type IVb hypersensitivity reactions performed by Th2-type (IL-4 & IL-5 [Interleukin-4

Table 1. Laboratory data of the patient

	Test	Result	Unit	Normal
Hematology	Complete blood count	-	-	-
	WBC	6400	mm^3	4000-11000
	Neutrophils	65	%	50-70
	Lymphocytes	30	%	15-35
	Monocytes	3	%	4-10
	Eosinophils	2	%	0-7
	Red blood cell	5.01	Million/mm^3	4.4-5.9
	Hemoglobin	14.6	g/dL	13-17
	Hematocrit	45.6	%	39-51
	Mean corpuscular volume	91	fL	78-94
	Mean cell hemoglobin	29	Pg	26-33
	Mean corpuscular hemoglobin concentration	32	g/dL	31-36
	Platelets	265	1000/mm^3	150-450
	Erythrocyte sedimentation rate 1 h	12	mm	0-20
Biochemistry	Fasting blood sugar	89	mg/dl	<140
	HbA1c	5	%	Normal: <5.7
	Urea	37	mg/dL	17-43
	Creatinine	1.0	mg/dL	0.7-1.4
	Total Cholesterol	124	mg/dL	Desirable: <200
	Triglycerides	101	mg/dL	Desirable: <150
	High-density lipoproteins	44	mg/dL	No risk:>60 Moderate risk: 40-60 High risk: <40
	Low-density lipoproteins	60	mg/dL	Desirable:<130
	Aspartate transaminase	23	U/L	<37
	Alanine transaminase	17	U/L	<41
	Alkaline phosphatase	180	U/L	80-306
	Lactate dehydrogenase	228	U/L	<480
Serology and Immunology	C-reactive protein	Negative	-	Negative
	Herpes simplex virus (IgG)	20.60	RU/mL	Immune: >10 Non immune: <10
	Herpes simplex virus (IgM)	0.24	Index	Positive: >1.1 Negative: <0.9 Borderline: 0.9-1.1
Hormone assay	Vitamin D	22	ng/mL	40-50

& Interleukin-5]) [5, 15]. Taking a comprehensive drug history and clinical examination helps find out the etiology of EM and appropriate management. Based on our experience, local corticosteroids are effective drugs for attenuating the complications and local lesions induced by the combination of sildenafil and tramadol.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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Authors' contributions

Conceptualization: Amirhossein Ghanbarzamani, Ebrahim Salehifar, Kaveh Kazemian; Methodology, writing – original draft, resources, and writing – review & editing: Amirhossein Ghanbarzamani, Ebrahim Salehifar, Kaveh Kazemian; Investigation: Amirhossein Ghanbarzamani, Kaveh Kazemian; Supervision: Amirhossein Ghanbarzamani.

Conflict of interest

The authors declared no conflicts of interest

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