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Erythema multiforme caused by sildenafil in an HIV(+) subject

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Key words
Sildenafil, HIV, drug-allergy, erythema multiforme, patch-test

Summary
Erythema multiforme is mainly caused by drug allergy and infections. This is the case of a HIV-positive, 49-year-old male, recently cured for syphilis, that presented erythema multiforme minor, five days after taking sildenafil. He had a fast recovery, only with the use of antihistamines. Cell-mediated allergy to sildenafil was confirmed six months later, with the use of patch-tests.

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Introduction

Erythema multiforme (EM) is an acute, self-limited skin eruption, mainly caused by infections and drug allergy (1). It is considered a type IV hypersensitivity reaction and its manifestations are within a wide spectrum of severity, summarized in a 'minor' vs 'major' classification. Viral (most commonly HSV), bacterial (Mycoplasma pneumoniae) and fungal infections (histoplasmosis) are precipitating factors of EM (1).
EM is rarely related to HIV and is not a common manifestation of drug allergy to antiretrovirals (2). Setting the diagnosis of EM in an HIV(+) patient can be challenging and anamnesis is its cornerstone.
The following is the case of an HIV-positive patient that presented EM minor, five days after the use of sildenafil.

Case report

A 49-year-old male was referred to my Allergy Clinic due to pruritus and mild erythema, limited to palms and feet, occurring for about twelve hours. No other symptoms were reported and no abnormal signs were noticed upon physical examination. He had been diagnosed with HIV four years before, with his first CD4 cell count being very low (52/mm^3). Soon after the diagnosis HAART treatment was prescribed, including tenofovir plus emtricitabine (co-formulated), atazanavir and ritonavir. The patient was still under the same antiretroviral treatment and his latest CD4$^+$ count was 620/mm^3, with an undetectable HIV viral load.
He reported to have been treated with ceftriaxone two months earlier, for syphilis. Such therapy had been completed more

than 45 days before, so the correlation of the antibiotic with the appearance of dermatitis was rather improbable. Two days before the appearance of the dermatitis he had used a new body lotion, so contact dermatitis was suspected, although the problem was limited to the extremities. Cetirizine (10mg/once daily) was prescribed and he was given instructions not to use the lotion and to be re-examined if dermatitis insisted.

The next morning he woke up due to intense pruritus and he soon noticed an extensive maculopapular rash, covering the extremities, abdomen, thorax and gluteal region, less extended to his back and neck. He was soon re-examined; besides the diffuse morbilliform eruption, a single target-lesion was detected in his right palm. No facial involvement was noted but there were oral mucosal lesions, causing a tingling sensation. No epidermal detachment or blisters were detected. The diagnosis of erythema multiforme was set and blood tests (complete blood count, a comprehensive metabolic panel, ESR and HSV 1 & 2 serology) were ordered.

When anamnesis was asked again he reported having used a tablet of sildenafil 100 mg, as an aphrodisiac, five days before the initial rush. He recalled having used sildenafil just once again, one year ago. Since herpes is often the cause of EM he was asked for herpes labialis, but he reported that he had no signs of it, at least during the previous six months.

He was released with cetirizine 10mg/twice daily for 7 days and a cream containing polidocanol and urea. He was advised to communicate promptly in the case that any vesicles would appear. His blood tests resulted to be normal.

He was re-examined 3 days later and skin's improvement was obvious, while pruritus was mentioned to be much milder. The total duration of the lesions was less than two weeks.

A patch test was performed, six months after the initial diagnosis, using sildenafil at 10% in petrolatum. It resulted positive confirming a cell-mediated drug allergy.

Discussion

The initial appearance of symmetrical maculopapular and "target" lesions on the extremities is typical in EM, usually spreading from acral to proximal areas and finally to the trunk. The pruritic -limited to the extremities- erythema, observed as first symptom in our case, was atypical for EM, while it is common in irritant or allergic contact dermatitis.

HIV-infected patients have a higher risk of developing cutaneous reactions, presumably as a result of immune dysregulation and altered drug metabolism (2). Antiretroviral drugs, as well as other medications, are often the etiology of EM in HIV-positive patients (2, 3). Antiretroviral therapy may cause various allergic skin reactions -from mild maculopapular lesions to toxic epidermal necrolysis (TEN)- but these reactions usually develop within the first 10 weeks of the initiation of therapy (2). The regular daily uptake of antiretroviral medications makes antiretrovirals an unlikely cause of drug allergy. On the contrary discontinuation of these drugs has been reported to cause EM as a result of viral replication (3).

Treponema pallidum has also been reported to cause EM, while secondary syphilis may also present with signs resembling EM, in HIV-positive patients (4-6). In such cases distinguishing EM due to *Treponema pallidum* from secondary syphilis, offers an intriguing differential diagnosis to the clinician. Nevertheless, all cases of HIV-positive patients with EM or EM-like symptoms associated with syphilis, resolve only after the use of antibiotics (4-6). In our case repeating antibiotics might have been an alternative in the case that lesions would not resolve fast, just by the use of antihistamines. It appears that treatment for syphilis had been successful for our patient and that syphilis was not related with the occurrence of EM, two months later.

Although allergic reactions to sildenafil are rare, a single case of TEN after a high intake of it has been published (7). Ours is the first case of EM associated with sildenafil. The time lapse of EM's onset, the lack of other newly-introduced drugs and the absence of an infection during the last weeks, drove to the diagnosis. Antihistamines controlled the pruritus and have probably helped to accelerate the anyhow self-limiting course of EM (1).

Serology for HSV types 1 and 2 can help to set the diagnosis in many EM cases, specially when a relavant recent anamnesis is reported, however they are not considered necessary (1, 8). Recurrent attacks of EM are expected in HSV-positive cases, requiring prevention with acyclovir (8). Skin biopsy is indicated only in persisting cases and can set the diagnosis in EM and EM-like eruption associated with *Treponema pallidum* (4, 5). When bacteria are the infectious agents, the use of antibiotics is necessary, offering a prompt resolution of the skin lesions.

In non-IgE mediated drug allergies, no well-standardized allergy tests exist for each drug. In order to confirm the diagnosis general instructions on patch testing for non-immediate drug eruptions were followed, and were proved to be useful (9). Theoretically immunodeficiency might affect the outcome of patch tests, however they are successfully used in HIV(+) patients (10). Other tests for cell-mediated allergy, like the lymphocyte transformation test, may be more reliable.

Stopping drugs, if feasible, is a first step to the diagnosis. However, stopping or switching antiretrovirals in the case of EM can be tried only during the first months of their introduction. The same practice stands also for other medications of regular-daily intake, while antibiotics or other drugs used occasionally, are more likely to cause drug allergy.

Concluding, clinical examination and anamnesis are the cornerstone of drug allergy diagnosis, specially when there are limited laboratory exams to confirm it.

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