Annular erythema and photosensitivity as manifestations of efavirenz-induced cutaneous reactions: a review of five consecutive cases

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Objectives: In HIV-infected persons, a rash is the most common manifestation of drug hypersensitivity reactions. Non-nucleotide reverse transcriptase inhibitors are a major cause of cutaneous reactions. While the characteristics of nevirapine-associated cutaneous adverse drug reactions (CADRs) have been well described, there are limited data on efavirenz-associated CADRs. The objective of this study was to characterize the clinical features of consecutive cases of efavirenz-associated CADRs in a single referral centre diagnosed over a 3 year period.

Methods: We retrospectively reviewed the clinical records of 231 patients admitted with CADRs to a tertiary dermatology ward in Cape Town, South Africa.

Results: In 42/231 (18%) cases, there had been exposure to efavirenz in the preceding 8 weeks. Of these, 5/42 (12%) patients were diagnosed with probable efavirenz-associated CADRs based on the Naranjo score. The median exposure to efavirenz before the onset of the rash was 12 days (range 2–48). All the patients were female, with a median age of 31 years and a median CD4 cell count of 300 cells/mm³ (range 81–887). Four had a photo-distributed eruption and one had a confluent indurated erythema affecting the face, trunk and limbs. In three out of five cases, there were annular plaques with raised erythematous edges and dusky centres, which were photo-distributed. Two patients had a mild transaminitis and another a mild eosinophilia. Histological features were non-specific, with perivascular lymphocytes the only consistent feature. In all five cases, efavirenz was withdrawn and potent topical steroid was the only CADR-specific intervention. The eruptions resolved on discharge from hospital, with no sequelae except for residual post-inflammatory hyperpigmentation.

Conclusions: Photo-distribution and annular erythema should alert clinicians to the possibility of efavirenz-associated CADRs.

Keywords: HIV, drug eruptions, photo-distribution

Introduction

In HIV-infected persons on antiretroviral therapy (ART), a rash is the most common manifestation of drug hypersensitivity reactions.1,2 The eruptions range from mild and transient to life-threatening, with 2%–10% of cases associated with an interruption or termination of therapy.1 The non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz, nevirapine and etravirine are major offenders and cause cutaneous reactions in 10%–17% of all those who start taking them.6

The characteristics of nevirapine-associated cutaneous adverse drug reactions (CADRs) have been well described; however, there are limited data on efavirenz-associated CADRs, which are less frequently encountered.4 Efavirenz-associated CADRs are commonly mild, while severe eruptions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) occur in 0.1% of patients, compared with a figure of 0.3%–1% reported for patients with nevirapine.5 The literature characterizing efavirenz-associated CADRs contains mainly case reports with a limited description of the rash.5–8

Here we describe the clinical features of five consecutive patients diagnosed with efavirenz-associated CADRs at a single referral centre between 1 January 2009 and 31 December 2012.

Methods

Study setting

The study population was patients presenting with CADRs to a dermatology ward at Groote Schuur Hospital, a tertiary referral centre in Cape Town,
South Africa. The hospital is one of two serving the population of Cape Town (~3.7 million individuals) through primary healthcare clinics and district and secondary hospitals.9

Participants and data extraction
We retrospectively reviewed the clinical records of patients admitted with CADRs to the dermatology ward from 1 January 2009 to 31 December 2012. Patients diagnosed with efavirenz-associated CADRs were included in the study. The following data parameters were extracted from the records: age, sex, CD4 cell count, drugs used and initiated in the preceding 8 weeks, duration of exposure to ART, clinical and laboratory parameters, management and outcomes. We further reviewed photographs and histology slides of the cases.

Definition of CADRs
CADRs include the spectrum of drug hypersensitivity syndrome (DHS), SJS, TEN and lichenoid and fixed drug eruptions. Photo-distributed drug eruption was defined as being well demarcated and most prominent on the exposed areas, these being the face, the back of the neck, the ears, the ‘V’ of the chest, the outer arms, the dorsa of the hands and the lower legs, in the context of initiation of a drug in the preceding 8 weeks.10 At least one consultant dermatologist made the diagnosis of CADR, based on the clinical and morphological features. The validated Naranjo score was used to assess the probability of efavirenz being the offending drug. This score is based on the pattern of response, the temporal relationship with the drug, withdrawal of the drug, rechallenge with the drug, alternative causes, placebo response, drug levels in the body fluids or tissues, the dose–response relationship, previous patient experience with the drug and confirmation by objective evidence.11

Ethics
All subjects gave written consent for the images to be published and to be included in the study.

Results
Demographic characteristics
We admitted 231 patients with a CADR during the study period. In 42/231 (18%) cases, there had been exposure to efavirenz in the preceding 8 weeks. Of these, 5/42 (12%) were diagnosed with probable efavirenz-associated CADRs based on the Naranjo score. In these five cases, the median duration of exposure to efavirenz before the onset of the rash was 12 days (range 2–48 days) and none had any previous recorded exposure to NNRTIs. All five patients were women, with a median age of 31 years (range 26–44 years). The median CD4 count was 300 cells/mm³ (range 81–887 cells/mm³). In the remaining 37/42 who had been exposed to efavirenz, CADRs were not clinically attributable to efavirenz in terms of the temporal relationship between the onset of the rash and the initiation of efavirenz, and the fact that efavirenz was continued through the drug reaction.

Clinical and laboratory characteristics
The clinical features of the five cases are summarized in Table 1. Four had a photo-distributed eruption and one had a confluent indurated erythema affecting the face, trunk and limbs. Of the photo-distributed cases, three had annular plaques with raised erythematous edges and dusky centres, and, in addition, there were tense blisters in Case 4 (Figure 1). All five had indurated tender palmar erythema. Interestingly, the erythema in Patient 2, who was 36 weeks pregnant on admission, continued to extend for 18 days after stopping efavirenz and had a leading erythematous edge, trailing scale and residual post-inflammatory hyperpigmentation (Figure 2). Two patients had a mild transaminitis and another a mild eosinophilia (all values being less than twice the upper limit of normal). The remaining blood counts and liver and renal functions were normal. The histological features were non-specific in four out of five cases, with a perivascular lymphocytic infiltrate the only consistent feature (Table 1). Case 4, with tense blisters on a background of annular lesions, showed no epidermal necrosis or vacuolar degeneration.

In all five cases, efavirenz was withdrawn and potent topical steroid was the only CADR-specific intervention. The mean duration of hospitalization was 9 days (range 4–18 days). The eruptions resolved on discharge without any sequelae except for residual post-inflammatory hyperpigmentation.

Discussion
In this retrospective study, we have identified annular erythema and photo-distributed eruption as major features of efavirenz-associated CADRs. The histological findings are non-specific, and there are no significant systemic features.

Annular erythema is associated with many conditions in dermatology, some of which are drug associated.12 To our knowledge, however, this is the first report of efavirenz-associated annular erythema. Larger prospective studies are needed to confirm our findings.

Photo-distributed reactions to efavirenz have previously been reported, and in our series four out of five cases were photo-distributed.13 To our knowledge, none of the other NNRTIs has previously been associated with photo-distributed eruptions, and this seems to be unique to efavirenz. Our findings further support photosensitivity as a manifestation of efavirenz hypersensitivity. HIV infection itself is, however, associated with higher odds of photosensitivity, which can be a presenting feature of the disease.14,15 It is thus important to exclude HIV-associated chronic actinic dermatitis as well as porphyria cutanea tarda, which we excluded clinically and histologically, when a photo-distributed drug eruption is suspected.

The absence of significant systemic symptoms in our series puts into question the prudence of stopping efavirenz. It is not clear whether these presumably mild reactions are transient or are an early manifestation of more severe life-threatening eruptions such as SJS, TEN and drug reaction with eosinophilia and systemic symptoms (‘DRESS’). SJS and TEN, and erythema multiforme were part of the differential diagnosis for the patient with blisters, but the absence of epidermal necrosis and vacuolar degeneration, respectively, ruled them out. With the increasing choice of ART available, the need to persist with efavirenz following any form of CADR seems difficult to justify.

There are several limitations of our findings, including those inherently associated with a retrospective study. The diagnosis of drug hypersensitivity is complicated and involves an analysis of a constellation of clinical and laboratory features. Our patients
were receiving drugs other than efavirenz and the reactions could be attributable to any of them. However, our use of the Naranjo score puts our findings into context, and we identified efavirenz as the probable cause in all five cases. The small number of cases involved makes it difficult to generalize our findings; to our knowledge, however, this is the largest study to characterize efavirenz-associated CADRs. Our cases were consecutive and treated at a single centre by a small group of doctors experienced in the management of CADRs, giving relative uniformity to the case definitions and management plan.

In summary, we have characterized efavirenz-associated CADRs in five consecutive cases. The most common clinical presentations were a photo-distributed eruption and annular plaques with raised erythematous edges and dusky centres. Photo-distribution and annular erythema should alert clinicians to efavirenz-associated CADRs. Larger prospective studies are needed to confirm our findings.

Table 1. Characteristics of five cases of efavirenz-associated CADR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous antiretroviral regimen</td>
<td>none</td>
<td>ZDV</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Drugs used in the 8 weeks preceding the CADRs</td>
<td>TDF, 3TC, EFV</td>
<td>ZDV, TDF, 3TC, EFV</td>
<td>TDF, 3TC, EFV, co-trimoxazole</td>
<td>TDF, 3TC, EFV, RIF, INH, pyrazinamide, ethambutol, co-trimoxazole</td>
<td>TDF, emtricitabine, EFV</td>
</tr>
<tr>
<td>Drugs initiated in the 8 weeks preceding the CADRs</td>
<td>TDF, 3TC, EFV</td>
<td>ZDV, TDF, 3TC, EFV</td>
<td>TDF, 3TC, EFV</td>
<td>TDF, 3TC, EFV</td>
<td>TDF, emtricitabine, EFV</td>
</tr>
<tr>
<td>Median duration of exposure to EFV before onset of the rash (days)</td>
<td>2</td>
<td>17</td>
<td>12</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Clinical features of CADRs</td>
<td>photo-distributed indurated plaques with scale; annular with erythematous edge and dusky centre; tender erythematous induration of the palms</td>
<td>photo-distributed indurated plaques with scale; annular with erythematous edge and dusky centre; tender erythematous induration of the palms</td>
<td>erythematous indurated plaques with scale on the trunk, limbs and face; tender erythematous induration of the palms</td>
<td>photo-distributed indurated plaques; annular, plaques with tense blistering predominantly at the edges and a dusky centre</td>
<td>photo-distributed erythematous scaly plaques</td>
</tr>
<tr>
<td>Histological features of CADRs</td>
<td>basket-weave hyperkeratosis; superficial perivascular lymphocytic infiltrate; band-like, interstitial lymphocytic infiltrate; isolated apoptotic keratinocytes</td>
<td>sparse perivascular lymphocytic infiltrate</td>
<td>focal parakeratosis; basket-weave hyperkeratosis; superficial and deep perivascular lymphocytic infiltrate; extravasation of red blood cells; interstitial lymphocytes; occasional eosinophils</td>
<td>mild spongiosis; subepidermal unilocular blisters with eosinophils in the blisters; basket-weave hyperkeratosis; eosinophils in the papillary and reticular dermis; perivascular and interstitial lymphocytic infiltrate</td>
<td>no histology</td>
</tr>
<tr>
<td>Discharge ART</td>
<td>TDF, 3TC, lopinavir/ritonavir</td>
<td>TDF, 3TC, lopinavir/ritonavir</td>
<td>TDF, 3TC, lopinavir/ritonavir</td>
<td>TDF, 3TC, lopinavir/ritonavir</td>
<td>TDF, ritonavir, atazanavir</td>
</tr>
</tbody>
</table>

EFV, efavirenz; 3TC, lamivudine; TDF, tenofovir; ZDV, zidovudine; RIF, rifampicin; INH, isoniazid.
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Transparency declarations
None to declare.

References