Clinical Case

Cutaneous rash following nevirapine initiation: what if not allergic reaction?

Summary
In the last 15 years, anti-HIV multitherapies have become potent enough for reduce the viral replication and prolonged its inhibition. Amongst the specific toxicities cited for HAART, exanthemas represent the most frequent cutaneous adverse events. The Authors report a diagnostic misunderstanding of a cutaneous rash in an homosexual HIV-positive man treated with nevirapine, highlighting the anamnestic, clinical and laboratory findings that allowed a correct unexpected diagnosis.

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In the last 15 years, anti-HIV multitherapies have become potent enough for complete and prolonged inhibition of viral replication and reconstitution of the immune system, remarkably improving life expectancy among HIV-infected subjects. Multidrug regimens, often referred to as HAART (Highly Active Anti-Retroviral Therapy), comprise two nucleoside reverse transcriptase inhibitors (NRTIs) and a HIV protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Specific toxicities cited for HAART include numerous mucocutaneous reactions, amongst that exanthemas represent the most frequent cutaneous adverse events. Although all classes of antiretroviral drugs may be responsible for rashes, NNRTIs (and nevirapine -NVR- in particular) are known to cause the highest incidence of morbilliform eruptions during the first 6 weeks of therapy[1]. Patients receiving NVR and exhibiting cutaneous eruptions must be closely observed because in as many as 8% disease may progress to hypersensitivity or Stevens-Johnson syndrome. Major risk factors seem to be a high CD4 cell count, the female sex and the presence of systemic symptoms[1]. Adverse effects of NVR may also involve the oral mucosa[2].

Hereafter we report the occurrence of a cutaneous rash in a homosexual HIV patient treated with NVR, highlighting the anamnestic, clinical and laboratory findings that allowed a correct unexpected diagnosis.

In November 2009, a 34-year-old homosexual

HIV-positive man presented to our center for a non-pruritic skin rash. The rash had appeared on his abdomen and progressively spread. On examination 1-2 cm round macules and papules, pale pink to red in colour, were seen on the trunk, upper limbs (figure 1) and neck with some tendency to coalescence. Palms and soles were spared, but white patches were seen on the pharynx mucosa (figure 2).

HIV infection had been previously disclosed in July 2005, but the patient was asymptomatic since that time. Viral load had maintained lower than 10000 UI/ml and CD4 cell count had always stayed around 600 cell/mL, therefore antiretroviral treatment had not ever been initiated.

Figure 1. Maculo-papular rash on the trunk.

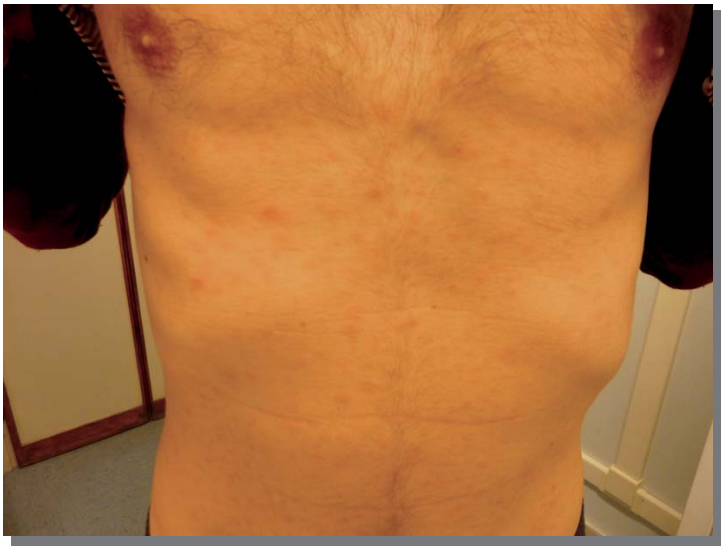
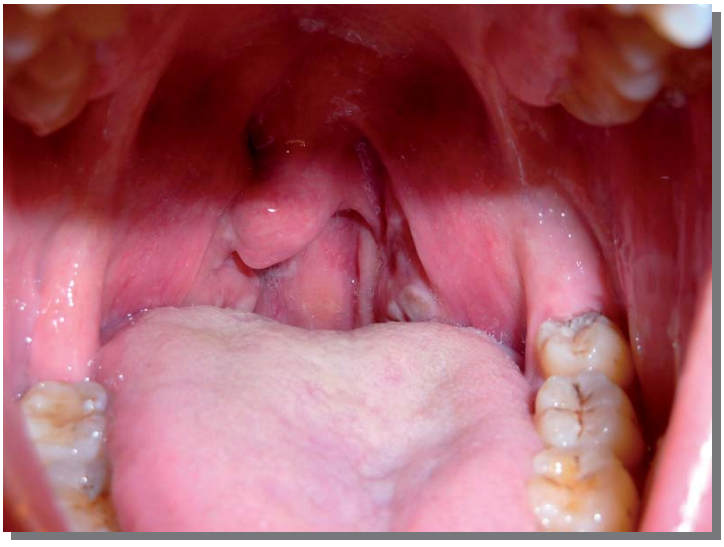


Figure 2. White patches on the pharynx mucosa.



However, in September 2009, viral load had shown an abrupt increase (718000 UI/ml) paralleling a significant decline of CD4 cells (335/mL). According to the current Guidelines of the DHHS Panel[3] and the results of resistance assays (the patient was unfortunately resistant to efavirenz), HAART was initiated with tenofovir and emtricitabine in combination, 1 pill daily, plus nevirapine , the last at the starting dose of 200 mg per day for 2 weeks then increased to the standard 400 mg per day. At that time serology for syphilis, *Chlamydia Trachomatis*, HSV and viral hepatitis were negative.

It was three weeks after starting the drugs that the exanthema appeared. The patient showed a generalized nontender lymphoadenopathy, without fever or other symptoms. He denied unprotected sexual intercourses and genital or oral ulcerations in the previous 6 months, but further enquiries revealed unsafe oral contacts with multiple partners. Therefore the evaluation of viral infections gave negative results; on the opposite syphilis serology finally showed positive VDRL and TPHA 1:1280. A diagnosis of secondary syphilis was made and the patient was treated with 3 weekly intramuscular injections of 2,4 million units of benzathine penicillin. At 2-week follow-up visit the exanthema had cleared. The patient is currently under HAART and repeated VDRL tests are negative, indicating a response to penicillin therapy.

In this report, we described a case of secondary syphilis in a MSM who had begun HAART for worsening immunodeficiency due to HIV infection.

Syphilis is a chronic systemic venereal disease with protean clinical features caused by the microaerophilic spirochete *Treponema pallidum*. The natural history of the disease is classified in stages (primary, secondary and tertiary syphilis) intervening between variable periods of latency. Since syphilis and HIV are both transmitted sexually, it's not surprising that a consistent proportion of patients are infected with

both agents. The majority of these cases are men who have sex with men (MSM) and detailed analyses have revealed that unprotected oral sex is the main risk factor for syphilis transmission among gay HIV-positive men. Nevertheless the co-infection is often very challenging for medical practitioners by means of atypical clinical presentation of syphilis in HIV subjects, atypical evolution and length of stages, difficulties in the interpretation of serological tests, potential neurosyphilis and choice of the treatment[4].

In our case, the strict time relationship between HAART initiation and the emergence of cutaneous rash had initially suggested the hypothesis of an adverse reaction to antiretroviral therapy. Besides, other points seemed to support this diagnosis: first, the patient was assuming a specific drug combination containing NVR (the NNRTI most frequently associated with skin eruptions); second, the latency of about 3 weeks was consistent with an adverse drug reaction; third, the clinical features and evolution could mimic a drug exanthema.

In the drug eruption, in fact, as in our patient, erythematous roundish lesions, somewhere figuring patches, develop on the trunk and spread to the limbs. Moreover, a recent case has been reported by Moura[5] in which NVR had determined the development of a white plaque on the buccal mucosa, very similar to that observed in our patient.

Nevertheless the presence of diffuse lymphadenopathy made us consider syphilis, despite patient's denial about risk sexual behaviour, the inapparent primary chancre and negativity of recent laboratory tests.

Serology allowed us at last to make the correct diagnosis and therefore we could also diagnose properly the lesion of the pharynx as an "opaline papule". Opaline papules are a kind of white lesions consisting of round silver-gray erosions with a red areola involving the palate, pharynx, larynx, glans penis, vulva or anal canal and rectum, rarely seen in secondary syphilis[6].

As is known, syphilis is historically defined as "the great mimicker", simulating numerous skin diseases; moreover when syphilis occurs in HIV patients polymorphism and atypical time evolution can be even more pronounced[7,8]. Scarce reports however can be found in the recent literature regarding syphilitic rashes resembling drug allergy[9] or vice versa[10]. Besides, in none of them the putative causative drug was an antiretroviral agent, that sounds strange considering the high rate of co-infection.

In conclusion our case is reported to remind the difficulties of a correct diagnosis of syphilis in some cases and the necessity to consider repeatedly this diagnosis in HIV patients receiving HAART and experiencing skin rashes, even when anamnestic and clinical findings might suggest a drug reaction. **TiM**

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