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LETTERS TO THE EDITOR

Parsonage—Turner syndrome: A rare case of abacavir hypersensitivity reaction in HIV-infected patients

We report a case of Parsonage—Turner syndrome occurred during abacavir hypersensitivity reaction (ABC-HSR) in an HIV-1-infected patient.

A 35-year-old Caucasian man presented with blue nodules in the buccal cavity. Prior medical history was significant for a syphilis infection treated with parenteral diaminocillin in 1995.

On examination, he was fine and no abnormalities were found except for two blue nodules in the buccal cavity. During blood examination, HIV-1 Ab resulted positive (the previous test performed on 1995, during syphilis infection, resulted negative), the CD4 cells' count was 633/μl (22%) and HIV-RNA was 82,000 copies/ml. Serological and molecular tests for human herpes virus 8 (HHV-8) resulted positive. At nodules' biopsy, a Kaposi's sarcoma was diagnosed. Total body CT scan, gastroscopy and colonoscopy resulted negative for secondary Kaposi's localizations. At the HIV-1 genotype assay, a large amount of secondary mutations, consistent with the evolution of a primary wild type HIV strain, were detected. Three months after HIV diagnosis, a highly active antiretroviral therapy (HAART) regimen with lopinavir/ritonavir (400/100 mg twice a day), abacavir (300 mg twice a day) and lamivudine (300 mg once a day) was started according to guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.[1]

Two weeks after HAART beginning, the patient reported fever, pharyngodynia and maculopapular skin rash. A generalist diagnosed an acute bacterial pharyngitis and empirical treatment with paracetamol and amoxicillin/clavulanate was started. Four days later, because of fever and skin rash persistence and appearance of swelling of superficial lymph nodes, patient stopped amoxicillin/clavulanate and was hospitalised. At admission, the patient was febrile (38 °C) and presented spotted erythema, swelling of superficial lymph nodes and sore throat. Blood examination showed values for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) higher than 200 UI/ml; leucocytes' count was 10,100 cells/mmc, neutrophils' count was 80%, no atypical lympho-monocytes were detected at smear, lactate dehydrogenase (LDH) and C-reactive protein (CRP) were increased but values for creatine phosphokinase (CPK) were normal. The CD4 cells' count was 640/μl (21%), HIV-RNA was 78,000 copies/ml. Chest X-ray, blood cultures, serology for CMV, HSV, EBV, Coxsackievirus, and influenza virus and rheumatic tests were performed and resulted negative. Because the symptoms worsened after each dose of abacavir, the clinicians supposed an abacavir hypersensitivity reaction and HAART was stopped. No additional therapy was administered.

One day after discontinuation of therapy, fever and skin rash resolved but patient presented right arm pain with increasing functional impotence and following right upper limb paresis without other neurological symptoms. Brain and spinal MRI did not show the presence of masses, lesions, radiculopathy or atrophy reportable to HIV-related opportunistic diseases or traumatisms. An electromyographic assay documented muscular damage on the triceps brachii. A double-energy X-ray absorptiometry (DEXA) total body scan did not show a reduction of spinal and scapular calcium level. At neurologist advice, a therapy with non-steroidal antiinflammatory drugs (FANS) and B1 and B6 vitamins was started. Gradually, the patient reported a reduction of paraesthesia and myalgias and then physiotherapy was started. One week later, blood examination documented a normalization of AST, ALT, leucocytes, LDH and CRP values. The pharmacogenomic test for *HLA-B*5701* allele was performed and resulted positive and a new antiretroviral therapy with tenofovir/emtricitabine and lopinavir/ritonavir was started. Three months later patient has further improved: CD4 cell count is 893 cells/μl, HIV viral load is below sensitivity limit (50 copies/ml), myalgias had fully disappeared but right shoulder and upper limb mobility was not completely restored, so physiotherapy continued. Six months later patient is fully recovered and antiretroviral therapy is simplified to tenofovir/emtricitabine plus atazanavir/ritonavir (300/100 mg daily).

Abacavir hypersensitivity reaction (ABC-HSR) has been reported in 5—8% of abacavir-treated patients during the first 6 weeks on abacavir (with a median time to onset of 11 days). Usually, patients present fever (80%), skin rash (70%) and asthenia (40%); sometimes, gastrointestinal (as nausea, vomiting, diarrhoea, and abdominal pain) or respiratory symptoms were reported; in 10% of the patients, myalgias, pains in the joints or myopathic symptoms have been referred.[2] Symptoms related to the hypersensitivity reaction worsen with continued therapy and usually improve within 24—72 h of abacavir discontinuation. Re-challenge with abacavir, after a hypersensitivity reaction, typically results in recurrence of symptoms within hours, with the potential to induce a more severe clinical syndrome with increased risk of life-threatening hypotension and death.[3—6] No correlations among CD4 cells' count, HIV-RNA levels, protease inhibitors (IPs) or non-nucleoside reverse transcriptase (NNRTIs) use and ABC-HSR risk or frequency

were found.[3] On the contrary, hypersensitivity reaction to abacavir is strongly associated with genetic factors such as the presence of the *HLA-B*5701* allele.[6]

The prevalence of *HLA-B*5701* allele is 5—7% in Caucasians and Hispanics, <1% in Africans.[7] The correlation between *HLA-B*5701* allele and ABC-HSR has been demonstrated for Caucasians and Hispanics but not for Africans, because of lowest prevalence of *HLA-B*5701* allele in African people. The results of SHAPE study demonstrated that, although ABC-HSR is uncommon in black persons, the 100% sensitivity of *HLA-B*5701* as a marker for ABC-HSR in both American white and black patients suggests similar implications of the association between *HLA-B*5701* positivity and risk of ABC-HSR in both races.[8] In a recent study, *HLA-B*5701* screening is shown to reduce the risk of ABC-HSR.[6] In predominantly white populations, 94% of patients do not carry the *HLA-B*5701* allele and are at low risk for ABC-HSR. However, not all *HLA-B*5701* positive patients will have a hypersensitivity reaction to abacavir.[6]

The Parsonage—Turner syndrome is an idiopathic neuritis of brachial plexus. The incidence rate for this syndrome is 1.5 cases/100,000 persons and young adult men were more frequently affected than women (2:1).[9] The Parsonage—Turner syndrome is often misdiagnosed and its causes are not known. Frequently, the onset of disease is subsequent to viral or bacterial infections, vaccine- or serum-therapy, surgery; but it also occurs during hypersensitivity reactions, with a possible immune-mediated pathogenesis.[10] Symptoms are various, but acute unilateral myalgias with predominant scapular cingulum impotence are characteristics. Patients present antalgic immobility and they develop complete scapular cingulum paresis in 2 weeks. Diagnosis is clinical, but sometimes EMG or muscular MRI can show acute axonal denervation and muscular edema (supraspinatus or subscapular). X-ray and spinal column MRI are generally normal. The differential diagnosis includes any muscular disease such as break, slipped disc, cervical spondylosis, malignant tumour, brachial plexus haemorrhage or lateral amyotrophic sclerosis. Purpose of the treatment is pain control: analgesics, steroids and immobilization are the gold standard. Prognosis is good and an early rehabilitation guarantees a faster recovery of symptoms.[9]

In our case, the ABC-HSR presentation is unusual. The onset of hypersensitivity reaction was common, with fever and skin rash, but successively the patient developed a variety of neurologic symptoms referable to Parsonage—Turner syndrome. As we know, there are few cases of Parsonage—Turner syndrome in HIV-infected patients. Some cases were described as occurring during the seroconversion stage of an HIV infection.[11,12] In our patient, HIV infection was already advanced, as evidenced by the diagnosis of Kaposi's sarcoma. The high CD4 cell count was not surprising, because it is known that patients with HIV-related Kaposi's sarcoma responded to HHV-8 antigens less often and had much lower HHV-8-specific T cells' count than did asymptomatic HHV-8 carriers, regardless of CD4 T-cell count. HIV-related Kaposi's sarcoma is associated with a lack of HHV-8-specific T cells but it is not related to CD4 cells' count.[13]

All microbiological, serological, biochemical and radiological tests performed resulted negative. The diagnosis of immune reconstitution inflammatory syndrome (IRIS) has been excluded since major and minor criteria for case definition were absent.[14] Allergic reactions to antiretroviral treatment as DRESS (drug rash with eosinophilia and systemic symptoms) or AGEP (acute generalized exanthematous pustulosis)[15] were also excluded since in our patient eosinophilia and pustules were absent. In our case we decided to stop abacavir therapy supposing an ABC-HSR. The pharmacogenomic test, successively performed, demonstrated the presence of *HLA-B*5701* allele and increased our hypothesis of Parsonage—Turner syndrome during abacavir hypersensitivity reaction.

*HLA-B*5701* screening had been demonstrated to reduce the risk of ABC-HSR. The Predict-1 study demonstrated that, in a predominantly white population, 94% of patients are *HLA-B*5701* allele negative and are at low risk for hypersensitivity reaction to abacavir. The genetic screening test for *HLA-B*5701* in the Predict-1 study demonstrated a negative predictive value of 100% and a positive predictive value of 47.9% for immunologically confirmed hypersensitivity reaction. For clinically diagnosed hypersensitivity reaction, the presence of the allele had a positive predictive value of 61.2% and a negative predictive value of 95.5%.[5] The fact that in the Predict-1 the 38.8% of *HLA-B*5701* carriers tolerated abacavir during a 6-week observation period without hypersensitivity reactions is consistent with previous evidence that abacavir stimulates an antigen-specific *HLA-B*5701*-restricted $CD8^+$ T-cell response and that *HLA-B*5701* is necessary, but not sufficient, for a hypersensitivity reaction.[6,16,17]

In the Predict-1 study, the epicutaneous patch testing had also been evaluated. This testing estimates a delayed hypersensitivity response to abacavir administration and addresses the problem of false positive clinical diagnosis by identifying patients who have had an immunologically mediated ABC-HSR. However, the epicutaneous patch testing cannot be used as a predictive screening in patients who have not previously ingested abacavir: a positive result of patch testing indicates a true immunologically mediated hypersensitivity reaction to abacavir, but a negative result can neither rule out the diagnosis nor be used for a re-challenge with abacavir.[6] In the Predict-1 study, all patients with a positive epicutaneous patch testing had a positive *HLA-B*5701*, providing further evidence that genetic screening has a high sensitivity for immunologically hypersensitivity reactions.[6,16,17]

In our case, the epicutaneous patch testing could confirm the hypothesis of Parsonage—Turner syndrome related to an abacavir hypersensitivity reaction, but this test is not routinely available in Italian hospitals. Moreover, the positivity of *HLA-B*5701* and the improvement of symptoms following the suspension of drug can add value to, but not to confirm, the diagnosis of Parsonage—Turner syndrome related to an abacavir hypersensitivity reaction.

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Trimethoprim—sulfamethoxazole induced erythrodermic psoriasis

In an issue of the journal published in 2006, Kocak et al.[1] reported the case of a patient who developed febrile neutropenia and severe thrombocytopenia with diffuse erythematous maculopapular rash after exposure to trimethoprim—sulfamethoxazole (TMP—SMX). The authors underlined that although the TMP—SMX combination is usually well-tolerated, it could also lead to serious, even fatal, adverse events. We report the case of a patient affected by plaque-type psoriasis undergoing treatment with cyclosporin who developed erythrodermic psoriasis after exposure to TMP—SMX. To our knowledge, this is the first case reporting this association in the development of erythrodermic psoriasis.

TMP—SMX is a combination chemotherapeutic agent able to inhibit two sequential steps of bacterial metabolism.[2] Current clinical uses of TMP—SMX include urinary, respiratory and gastrointestinal infections as well as prevention of infections in immunocompromised patients.[2] More frequent side effects of TMP—SMX are mild gastrointestinal symptoms, dose related bone marrow effects, liver failure, skin rash, sepsis-like and hypersensitivity reactions.[3] Skin rash or more severe skin reactions such as exfoliative dermatitis, the Stevens Johnson Syndrome, the Lyell Syndrome or toxic epidermal necrolysis, have been rarely reported.[4]

Erythrodermic psoriasis is a severe and disabling variant of psoriasis, with a reported prevalence among psoriatic patients ranging from 1.5 to 31%.[5] This variant most commonly evolves from a pre-existing chronic plaque-type psoriasis and, if untreated, may lead to serious morbidity and even mortality. Clinically, it is characterised by diffuse erythema and fine scaling involving all or almost all of the body surface area, commonly associated with chills, exudation, oedema, weight loss, pruritus and fever. Withdrawal of systemic and topical corticosteroids, drugs' reactions, over-treatment with tar or dithranol, PUVA phototoxic reaction, sun exposure, and emotional stress have been reported as precipitating and triggering factors.[6]

We report the case of a 50-year-old male patient, affected with plaque-type psoriasis since the age of 40,