Delayed Allergy to Isoniazid in an HIV-Infected Patient

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Abstract—HIV infection represents a risk factor for hypersensitivity reactions to antimicrobial drugs. We report the first case of delayed, cell-mediated, allergy to isoniazid in a 57-year-old HIV-infected patient, who developed a maculo-papular exanthema after 10-day treatment with isoniazid, etambutol, pyrazinamide and rifabutin. Patch test resulted positive for isoniazid. Graded challenges with the other aforementioned medications were performed, allowing the patient to complete the antitubercular treatment. The striking observation of this case is that the patient developed a cell-mediated hypersensitivity despite the low level of CD4+ T cell count (< 200 cells/μL).

Index Terms—delayed hypersensitivity, HIV, isoniazid, tuberculosis

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection represents a risk factor for the occurrence of hypersensitivity reactions (HRs) to antimicrobial drugs, particularly those used to treat tuberculosis (TB) such as isoniazid, pyrazinamide and rifampicin (1-2).

Some of these HRs occurs after 7-10 days of therapy, suggesting the involvement of T-cell-mediated hypersensitivity. The diagnosis and management of drug hypersensitivity in HIV-infected patients is particularly challenging since the therapeutic protocols are based on multiple medication regimens. We report the first well documented case of delayed, cell-mediated, allergy to isoniazid in a patient with (HIV) infection despite the low count of CD4 T cells.

We report the case of a 57-year-old man suffering from AIDS, C-3 stage (according to Centers for Disease Control and Prevention categorization (CDC) categorization) suffering from pulmonary TB who developed a generalized maculo-papular exanthema after 10 days therapy with isoniazid, etambutol, pyrazinamide and rifabutin. The discontinuation of anti-TB medication and the administration of steroids and antihistamines, led to the complete clinical resolution of signs and symptoms. Allergological evaluation was performed 4 weeks later. Patch tested with isoniazid, etambutol, pyrazinamide and rifabutin each at 30% in petrolatum (3), were performed. Patch tests were carried out using the commercial form of drugs. Patches were applied on the interscapular region, removed after 48 h and evaluated after 72 h. Patch results were scored according to European Network for Drug Allergy (ENDA) indications (4) faint erythema was considered as a doubtful reaction; erythema, induration and discrete papules a weak positive reaction (+); erythema, induration, papules and vesicles a strong positive reaction (++); intense erythema, induration and coalescing vesicles an extremely positive reaction (+++) (Fig. 1). Negative controls were performed with petrolatum.

Patch tested resulted positive only for isonizide. In order to prove that this was not a non-specific irritant response, 10 healthy subjects underwent the patch test with isonizide with negative results. Based on this findings, a diagnosis of delayed cell-mediated allergy to isoniazid was formulated. Patient underwent graded oral challenge with etambutol, pyrazinamide, rifabutin without any adverse reactions and tolerated the gradual reintroduction of this medications in his therapeutic regimen.

The frequency of drug-related reactions is higher in HIV-positive patients than in the general population. Drug used for the treatment of the virus and those used for opportunistic infection and complication of HIV are associated with many adverse effects.

Furthermore, about one third of HIV-infected patients suffer also from TB and its treatment can be particularly challenging because of interactions with antiretroviral drugs, paradoxical effects and hypersensitivity (2).

Isoniazid is reported to elicit hepatic and neurological adverse reactions and, less frequently, skin reactions (cutaneous eruptions, occupational contact dermatitis) (6). An underlying cell-mediated allergy (positive patch tests) has been demonstrated in a few immunocompetent patients (6,7).

To best of our knowledges, this is the first case of delayed, cell-mediated, allergy to isoniazid in an HIV-infected patient. Surprisingly, the patient developed a T-cell-mediated hypersensitivity despite a low level of CD4+ T cell count (< 200 cells/μL). The effector role of CD4+ T cell in delayed hypersensitivity is well assessed. Immunohistochemistry revealed that most infiltrating lymphocytes in maculopapular drug eruptions are CD4+ (8). They are present around the vessels in the dermis, but partly migrate to the epidermis and some even penetrate into the epidermis. CD8+ T cells are also found in most histological specimens but are present in lower numbers in the maculopapular exanthema. Contact sensitization, unlike other DTH reactions, is apparently drive...
predominantly by CD8+ lymphocytes, which are normal or increased in HIV infection (9). Likewise, cytotoxic CD8+ T cells can also act as effectors, playing a dominant role, in maculopapular or bullous skin diseases (10). CD8+ activated T cell can kill keratinocytes in a perforin/granzyme B and/or FasL-dependent manner. These reactions seem to be more severe because all the cells expressing MHC I may be possible targets for CD8+ T cells. Unfortunately we could not perform a biopsy as the patient refused. Furthermore our report confirms the importance of a step-wise exposure test when an adverse reaction occurs during a multiple medication regimen. This test allows to better understand the cause-effect relationship between the drug and the adverse event and enables the patient to take the drugs he needs. On the basis of the allergy testing our patient underwent provocation tests with all anti-TB drugs except for isoniazid. This provided the patient with a safe and effective treatment of active pulmonary TB. Delayed, cell-mediated, allergy may undelight hypersensitivity reaction also in patients with important reduction of CD4+ T cells. The identification of the causative agent and subsequent graded challenge with suspected not causative medication may improve the prognosis of AIDS affected patients who normally experience drug reactions ongoing multidrug therapeutic regimens.

Further studies on larger groups of patients are needed to better understand the mechanisms underlying drug hypersensitivity in HIV-infected patients.

REFERENCES


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