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LETTER TO THE EDITOR

INFLAMMATORY PARADOXICAL REACTION OCCURRING IN TUBERCULOSIS PATIENTS TREATED WITH HAART AND RIFAMPICIN

Rio de Janeiro, August 30, 2001

Dear Editor,

The introduction of highly active antiretroviral treatment (HAART) during tuberculosis treatment may be followed by a systemic inflammatory and paradoxical reaction with flare of symptoms and lymph node enlargement[4]. This reaction has also been observed in association with the treatment of disseminated *Mycobacterium avium* complex (MAC) infection[5], Cytomegalovirus and other opportunistic infections[6]. This paradoxical response has been attributed to a rapid recovery of the immune system, early during the treatment with HAART, in previously immunosuppressed patients, probably reflecting the redistribution of memory T-lymphocytes.

Rio de Janeiro is an endemic area for tuberculosis**,** with 120 cases in 100,000 inhabitants**,** and the most prevalent region for HIV/AIDS in Brazil[2]. We report in our Center a 34.2% prevalence of tuberculosis among AIDS patients[8]. Since 1997, the Brazilian's Ministry of Health gives antiretroviral treatment free of charges to all AIDS patients[4]. Tuberculosis, however, remained a great problem because of rifampicin interactions with protease inhibitors (PI) and non-nucleoside analogs (NNRT)[3]. Since March 2001 the association of HAART (ritonavir/saquinavir or efavirenz) and rifampicin was accepted by the CDC guidelines[5] and later by Brazilian Consensus Statement[2].

We observed 3 cases of inflammatory reaction among 8 tuberculosis and AIDS patients treated with HAART and rifampicin. Clinical and laboratory characteristics of patients with paradoxical reaction are presented**,** as follows:

Case 1: Female**,** 37 years, initial antiretroviral treatment with AZT and ddI one month before the inclusion in our protocol and naïve for TB treatment. Tuberculin test showed 55 mm induration. CD4 counts of 177 cells/mm^3 and viral load of 230000 copies/mL.TB was diagnosed by positive culture of cervical lymph node biopsy. Lymph node diameter of three cm before TB treatment was initiated with rifampicin, isoniazide and pyrazinamide. A new antiretroviral regimen was proposed 15 days after TB treatment had been initiated introducing efavirenz to AZT and ddI. Two months later this patient returned with a lymph node enlargement of 9 cm diameter, pain redness and local fluctuation. At that moment prednisone 40 mg/day was prescribed and a reduction in lymph node size was observed followed by fistulization and improvement of the paradoxical reaction. After one month, prednisone was suspended. All cultures obtained from lymph node drainage were negative for mycobacteria and fungus and TB treatment was maintained for nine months and withdrowed successfully. CD4 counts and viral load after HAART was respectivelly 328 cells/mm^3 and 44000 copies. In this case an optimal response to HAART was not achieved although CD4 counts presented a significant increase.

Case 2: Male**,** 37 years**,** naïve for TB and HIV treatments. Tuberculin test was non reactor. CD4 counts of 187 cells/mm^3 and viral load of 93618 copies/mL before treatment. TB was diagnosed by a positive culture of sputum (pulmonary tuberculosis concomitantly with a *Pneumocystis carinii* pneumonia). TB treatment was initiated with rifampicin, isoniazide and pyrazinamide. An antiretroviral treatment was proposed 45 days after TB treatment had been prescribed with efavirenz, AZT and 3TC. The paradoxical reaction was first observed two months after TB treatment (15 days after HAART) when we observed a huge enlargement in the right side of the neck and mediastinal lymph nodes. Talidomide was introduced with improvement 40 days after. A second episode three months after HAART was also detected with a compression of iliac venous branch by an inguinal lymph node and deep venous thrombosis. Prednisone 40 mg daily was prescribed and the paradoxical reaction controlled almost 30 days from it's start. CD4 counts and viral load after HAART were respectively 264 cells/mm^3 and below 80 copies/mL.

Case 3: Male**,** 27 years, naïve for TB treatment and previously treated with AZT and ddI a year before admission in our centre**.** Tuberculin test was non-reactor. CD4 counts and viral load before treatment of 38 cells/mm^3 and 43000 copies/mL respectively. Efavirenz was added to the previous regimen without any change in nucleoside analogs before coming to treat TB in our hospital. Pulmonary tuberculosis was diagnosed by visualization of acid fast bacilli and a positive culture in sputum. This case seemed milder than the first two ones. We observed a cervical lymph node enlargement (four cm diameter) with redness and fistulization. A non-hormonal antiinflammatory treatment was prescribed and the symptoms disappeared two weeks afterward. In this case, we did not achieve an optimal response to antiretrovirals after HAART (CD4 counts 62 cells/mm^3 and viral load 20000 copies), probably because of a previous mistake in this prescription. We just changed one nucleoside analog and a good virologic and immunologic response was achieved (viral load below 80 copies/mL and CD4 counts 127/mm^3)

Although none of these cases were fatal, we are very concerned about this inflammatory reaction. We are worried about increasing iatrogenic cerebral tuberculomas such as found in other description's[1,9] or to provoke, with HIV-TB treatment, a compression of biliary ducts or vital vessels.

How long will last that syndrome? Who are at risk to develop this syndrome? Would it be better to start antiretroviral treatment concomitantly with anti-tuberculous drugs rather then in a later stage?

A longer casuistic is necessary to evaluate the predictive factors and to clarify other questions in order to guide Brazilian and other underdeveloped countries' physicians in dealing with these non-desirable effects of HAART.

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