Revista da Sociedade Brasileira de Medicina Tropical
35(1): 59-61, jan-fev, 2002.

Paradoxical reaction to the treatment of tuberculosis uncovering previously silent meningeal disease

Reação paradoxal ao tratamento da tuberculose revelando doença meníngea previamente silenciosa

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Abstract *The development of paradoxical clinical worsening following initiation of tuberculosis treatment may complicate the clinical course of both HIV-infected and uninfected patients. We report a severe manifestation of the so called paradoxical reaction to the treatment of tuberculosis that unmasked previously silent meningeal disease in a 34-year-old HIV-infected male patient.*

Key-words: *AIDS. Antiretroviral therapy. Paradoxical reaction. Tuberculosis. Tuberculous meningitis.*

Resumo *O desenvolvimento de piora clínica paradoxal como resposta ao início do tratamento da tuberculose pode complicar a evolução de pacientes com e sem infecção pelo HIV. Apresentamos uma grave manifestação da chamada reação paradoxal ao tratamento da tuberculose, que revelou doença meníngea previamente silenciosa em um paciente HIV-positivo de 34 anos.*

Palavras-chaves: *AIDS. Meningite tuberculosa. Reação paradoxal. Terapia anti-retroviral. Tuberculose.*

Concomitantly treating active tuberculosis (TB) and HIV infection is a challenging task. There is a great potential for adverse effects and clinically significant pharmacological interactions. The development of paradoxical clinical worsening on TB treatment may further complicate patient management. We report a life-threatening manifestation of paradoxical worsening following TB treatment initiation in an antiretroviral (AR)-experienced patient.

CASE REPORT

A 34-year-old HIV-infected male patient with previous experience to the HIV reverse transcriptase inhibitors zidovudine and didanosine, to the HIV protease inhibitor saquinavir and on *Pneumocystis carinii* prophylaxis developed an enlarging cervical mass associated with a 2-month history of fever, weigh loss and malaise. At that point laboratory evaluation showed mild anemia (hemoglobin 11,3mg/dL), 60 CD4 cells/mm^3 and a plasma HIV viral load of 25,000 copies/mL (all viral load measurements were performed using the nucleic acid sequence-based amplification assay). Chest X-ray was normal. He had never had an opportunistic disorder but was treated for pleural TB during early adulthood. Histopathology disclosed TB lymphadenitis and *Mycobacterium tuberculosis* grew from the node aspirate. Rifabutin (as an alternative rifamycin to be combined with a protease inhibitor) at a dose of 150mg/day, isoniazid, pyridoxine and pyrazinamide were started and the AR regimen was changed to stavudine, lamivudine and indinavir. He significantly improved and remained well until ten weeks later when recrudescence of fever and severe headache developed. Signs of meningeal irritation were absent, as were cognitive, behavioral or focal neurologic abnormalities. Computed tomography of the brain was normal. Cerebrospinal fluid (CSF) studies revealed marked pleocytosis (220 cells/mm^3, 71% polymorphonuclear, 29% mononuclear cells), glucose 52mg/dL and elevated protein (156mg/dL) and were negative for acid-fast bacilli, mycobacterial cultures, other infectious agents and neoplastic cells. Ophthalmologic examination disclosed TB choroidal nodules (previous evaluations had been normal). A presumptive diagnosis of TB meningitis was made and the clinical picture was

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Presented in part, in poster form, at the XIII International Conference on AIDS, Durban, South Africa, 2000.
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Recebido para publicação em 19/2/2001.

considered consistent with a paradoxical response to therapy initiation. Prednisone and ethambutol were added to the above drugs. Headache slowly improved over the ensuing several weeks and the steroid was tapered until withdrawal 4 months later when CSF studies were entirely normal. He completed 14 months of TB therapy asymptomatic, with normal hemoglobin and resolution of the choroidal nodules. Shortly before completion of therapy the CD4 cell count was 170/mm^3 and the plasma viral load 17,000 copies/mL. Nine months later the CD4 count was 310/mm^3 and the viral load 19,000 copies/mL.

DISCUSSION

The paradoxical response to the TB treatment in our patient was of particular interest due to its life-threatening presentation, unmasking previously silent meningeal disease. Paradoxical worsening can occur in both HIV-uninfected[1 10 13 15] and infected[2 4 5 8 11 12] patients starting TB therapy and is generally attributed to a reconstituting host delayed hypersensitivity response with increased exposure to mycobacterial antigens under bactericidal therapy. Recrudescence of fever, enlarging adenopathies, worsening pulmonary infiltrates, pleural effusion, ascites, new or enlarging parenchymal central nervous system lesions and superior vena cava syndrome have all been reported[1 2 4 5 8 10-13 15]. We are unaware of previous reports of paradoxical responses uncovering meningeal disease in HIV-infected patients.

Such paradoxical worsening syndromes pose a diagnostic challenge because the apparent clinical deterioration may raise the suspicion of drug-resistant TB, noncompliance to the prescribed regimen or concomitant disorders unrelated to TB. These patients generally need no alteration in their drug regimen. At times, short-term steroid administration may be considered and was of great value in our patient.

Paradoxical worsening is by no means a recently observed complication of TB therapy initiation. In 1955 Choremis *et al*[3] reported that children starting TB therapy occasionally developed exacerbation of fever and X-ray findings. This phenomenon had been less frequently observed among children treated with streptomycin alone but markedly increased in frequency when combination therapy with streptomycin and isoniazid became standard of care. They acknowledged that the explanation for such a worsening was not easy but hypothesized that it might be related to *marked bacteriolysis and liberation of tuberculin in large amounts*[3].

In HIV-infected patients the syndrome of paradoxical worsening on TB treatment is not uncommon among those starting AR therapy and may well be considered a manifestation of the so called immune reconstitution syndrome. Narita *et al*[12] reported that a paradoxical reaction to TB treatment initiation occurred in 12 (36%) of 33 HIV-infected patients concomitantly initiating both therapies, in 2 (7%) of 28 HIV-infected patients treated for TB before the advent of AR therapy and in 1 (2%) of 55 HIV-uninfected patients starting anti-TB regimens[12]. Also, HIV-infected patients initiating both therapies are more prone to develop transient chest radiographic worsening than HIV-uninfected and HIV-infected patients not on AR therapy[4]. Enhancing host immunity following initiation of AR therapy or its intensification with a protease inhibitor has also been implicated in the emergence of cytomegalovirus retinitis[6], *Mycobacterium avium* complex lymphadenitis[14], development of zoster rash[9], rapid worsening of Kaposi's sarcoma lesions[7] and development of multiple cerebral lesions compatible with progressive multifocal leukoencephalopathy in AIDS patients[7].

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