Case report

DEVELOPMENT OF MULTIPLE ABSCESSSES IN AN HIV/TB CO-INFECTED PATIENT AFTER INITIATION OF ANTITUBERCULOUS AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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ABSTRACT

Since the use of Highly Active Antiretroviral Therapy (HAART) for HIV infection, there have been increasing reports of systemic manifestations of immune restoration. This new clinical syndrome among HIV-infected patients is associated with underlying co-infections with mycobacteria, cytomegalovirus, hepatitis B and C infections, etc… We report on an HIV/tuberculosis (TB) co-infected patient who developed an immune restoration inflammatory syndrome after initiation of HAART and anti-TB treatment. She developed fever, large abscesses and pleural and peritoneal effusions. Systemic symptoms decreased during corticosteroid treatment, but abscesses only disappeared 8 months after the start of the anti-TB treatment.

INTRODUCTION

Immune Restoration Inflammatory Syndrome (IRIS), also called Immune Restoration Disease (IRD), is now a well recognized disorder among HIV-infected patients after initiation of highly active antiretroviral therapy (HAART). It is postulated that HAART, by restoring immune functions, may promote the clinical expression or exacerbation of previously quiescent diseases (1,2). This phenomenon has been especially described in patients with underlying *Mycobacterium tuberculosis* (3-5), and *Mycobacterium avium* Complex (MAC) infections (6-9). According to a recent review by DeSimone et al. (1), systemic inflammatory reactions associated with HAART have been also reported in cytomegalovirus infection, hepatitis B and C infection, *Herpes zoster* infection, in patients with progressive multifocal leukoencephalopathy, cryptococcal meningitis, and even in patients with AIDS-related malignant conditions or auto-immune diseases. Symptoms related to IRIS (fever, general malaise, lymphadenopathies,...) are often aspecific, and could also be caused by other conditions such as opportunistic infections or drug-related adverse events.

Various clinical syndromes have been related to IRIS associated with mycobacterial diseases, including lymphadenitis and abscess formation, mostly caused by MAC infections (6-9). We report here on an HIV/TB co-infected patient who developed multiple lymph node abscesses, as well as pleural and peritoneal effusions during anti-TB treatment and HAART.

CASE REPORT

A 32-year-old Belgian woman, living in Indonesia for 6 years, was repatriated and admitted in February 2000 for recurrent diarrhoea and weight loss since 3 months, associated with abdominal pain and fever of

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one week duration. On physical examination she was cachectic (44 kg and 168 cm), and had a temperature of 38.8°C, several cervical and axillary painless lymph nodes (diameter of 2 cm), oral candidiasis and diffuse abdominal pain.

Laboratory data revealed an haemoglobin of 9.3 g/dl, a leucocyte cell count of 3260/ml, with 14.6% lymphocytes. The sedimentation rate was increased to 73 mm/hour and C-reactive protein to 13.6 mg/dl. Biochemistry showed a slight elevation of the liver enzymes (aspartate amino-transferase: 139 IU/L; alanine amino-transferase: 71 IU/L; alkaline phosphatase: 146 IU/L and gamma-glutamyltransferase: 251 IU/L) and a high level of lactate dehydrogenase (1392 IU/L). She was diagnosed as having an HIV-1 infection, with a CD4+ lymphocyte count of 19/mm³ (3.4%) and a viral load of >75000 copies/ml. Serological tests for hepatitis A, B, C and for syphilis were negative. A blood smear was negative for malaria. Blood and urine cultures remained negative while stool culture yielded an infection with Salmonella enteritidis.

A chest X-ray was normal. A Computed Tomographic (CT) scan of the abdomen revealed multiple enlarged sub-hepatic and para-aortic homogenous lymphadenopathies (diameter of 2 cm). Intravenous ciprofloxacin was started for the Salmonella enteritidis infection. Co-trimoxazole prophylaxis and antiretroviral therapy were initiated, including stavudine, lamivudine and indinavir. As fever persisted, a liver and bone marrow biopsy were performed. On histological examination granulomatous lesions containing acid-fast bacilli were observed and on culture a multi-drug sensitive Mycobacterium tuberculosis was grown. Two weeks after the initiation of HAART, anti-TB treatment was started, including rifabutin (150 mg daily), isoniazid (300 mg daily), ethambutol (1200 mg daily) and pyrazinamide (1500 mg daily). The daily dose of indinavir was increased to 1000 mg TID. The fever resolved completely 5 days later and the patient was discharged.

Two weeks later she was readmitted with high fever and abdominal pain. Physical examination revealed enlarged (3-4 cm) painful cervical, axillary, inguinal and epitrochlear lymph nodes and a painful epigastric tenderness. An abdominal CT scan showed a necrotising sub-hepatic abscess (diameter of 7 cm) and increased generalized abdominal lymph nodes. A large amount of ascitis and a large left pleural effusion were present, requiring evacuation by puncture. Mycobacterial cultures of these fluids remained negative. On the other hand aspiration of an axillary abscess 6 weeks after initiation of the anti-TB treatment showed the presence of acid-fast bacilli and a positive culture for Mycobacterium tuberculosis. Because of persistent fever HAART was stopped 7 weeks after its initiation.

The clinical condition of the patient improved and the fever disappeared. After a 2 week interruption of HAART the rifabutin was switched to rifampicin and stavudine, lamivudine and abacavir treatment was started. One week later, new abscesses developed and the fever reappeared. Prednisone (32 mg/day) was then initiated, with a rapid clinical improvement. However, abscesses continued to appear during the following months (Figure 1), some with spontaneous discharge, some requiring aspiration. Acid-fast bacilli were still found on direct examination of the pus 8 months after the start of the anti-TB treatment, but cultures remained negative. Corticosteroids were tapered slowly according to clinical symptoms. In December 2000 the patient’s general condition was good, she had gained 12 kg, her CD4+ lymphocyte count was 180/mm³ (13.9%) and the viral load 1600 copies/ml. In total the patient was treated with 2 months of quadritherapy followed by 10 months of bitherapy. No relapse has been observed during the year following the stop of the anti-TB treatment.

DISCUSSION

A “paradoxical response” during anti-TB treatment is a well recognized phenomenon occasionally reported in HIV-uninfected patients (5,10), and in AIDS patients before the introduction of HAART (11,12). Clinical presentations include paradoxical increases of tuberculous lymph nodes (13), or of cerebral tuberculosis (10,14), respiratory distress in patients with miliary or widespread pulmonary tuberculosis and transient worsening of TB meningitis (15). It has been suggested that the paradoxical response may be related to an immunologic process involving altered cell-mediated responsiveness in the context of mycobacterial killing during chemotherapy (16). Since the introduction of HAART, paradoxical responses in HIV/TB co-infected patients have been reported by many authors (4,5,17). These reactions are now considered as manifestations of IRIS, but the differences between the “old” paradoxical responses (not following HAART) and the “new” immune restoration diseases have never been clarified. Until now, only one prospective study has demonstrated a higher incidence of paradoxical reactions.
among AIDS patients treated simultaneously with anti-TB therapy and HAART (36%), than among those treated only with anti-tuberculous drugs (7%) (5). The same study also showed a temporal relationship between these reactions and the initiation of HAART. However, the link between HAART and paradoxical worsening of TB has been recently questioned in another prospective study, where no significant differences could be found (18). IRIS manifestations occur often before a substantial change in CD4+ lymphocyte counts is observed, suggesting that other factors may be involved, such as the redistribution of antigen-specific T-cells and/or Th2 cytokine-mediated reversal of immunosuppressive T-cells (19).

IRIS is generally considered as a benign and transient condition, even if severe complications have been occasionally reported (CMV vitritis, reactivation of hepatitis B or C infection). Our patient also presented with severe clinical manifestations, including abdominal abscesses, and a life-threatening pleural effusion. A purulent discharge of lymph nodes was noted up to 8 months after the start of anti-TB therapy and HAART, which is an exceptional observation. Several factors may explain such an unusual long course, including the high mycobacterial burden related to the disseminated tuberculosis, the delay in starting anti-TB treatment, the severe immune deficiency before the start of HAART and the vigorous immunological response to HAART in this antiretroviral treatment naive patient.

An important lesson of this observation is that patients, particularly those with severe immune deficiency should be screened carefully for the presence of opportunistic infections before initiating HAART. If tuberculosis is diagnosed TB treatment should be started before initiating HAART. However, in patients with a very low CD4+ count concomitant treatment with HAART should be considered in order to avoid development of new opportunistic infections. Such patients should be carefully monitored for development of IRIS and when IRIS manifestations occur corticosteroid treatment should be considered.

As antiretrovirals are now increasingly used in developing countries where TB/HIV co-infection is highly prevalent, it is likely that clinicians will be increasingly confronted with TB-related IRIS manifestations. Clinical and epidemiological studies are needed to determine the incidence of IRIS, to define diagnostic criteria and prognostic factors, and to investigate appropriate preventive measures and treatment.
SAMENVATTING

Sinds het gebruik van «Highly Active Antiretroviral Therapy (HAART)» voor de behandeling van HIV infectie wordt een stijgend aantal klinische verschijnselen beschreven te wijten aan een immuunrestitutie fenomeen. Dit nieuw klinisch syndroom bij personen met HIV infectie komt voor bij onderliggende co-infecties met mycobacteria, cytomegaalvirus, hepatitis B en C infecties, enz… Wij beschrijven een HIV/tuberculose (TB) gecoïncideerde patiënt die een inflammatoire syndroom ontwikkelde t.g.v. immuunrestitutie na het starten van HAART en anti-TB behandeling. Zij ontwikkelde koorts, belangrijke abcessen en een pleurale en peritoneale uitstorting. Algemene symptomen regresseerden tijdens behandeling met corticosteroiden maar de abcessen verdwenen slechts 8 maanden na het starten van de anti-TB behandeling.

REFERENCES