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EXTRAPULMONARY TUBERCULOSIS IN HIV INFECTED PATIENTS - A DIFFICULT TO CONTROL DISEASE

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Abstract. We would like to present the case of a 44-year old man, who was admitted and diagnosed in our hospital with HIV infection (stage C2) with abdominal tuberculosis as AIDS defining disease, oral candidiasis and deep venous thrombosis (tibial vein). We initiated standard tuberculostatic treatment with four first line drugs and after two weeks we started antiretroviral therapy (ARV) with Zidovudine (ZDV), Lamivudine (3TC) and Efavirenz (EFV). We recorded a rapid growth of CD4 to 296/mmc, with immune reconstitution syndrome (IRIS). In the next two weeks, the patient developed severe neuropsychiatric events most likely induced by EFV, ARV therapy thus ceased. Four months later with relative clinical favorable evolution a new viro-immunological evaluation was performed, with CD4 211/mmc and HIV RNA 5,9 log 10 cp/ml. ARV therapy was resumed with Abacavir (ABV), 3TC and Raltegravir (RAL) in double dose (800 mg BID) with good tolerance and rapid immunological and virological response. In conclusion, Raltegravir stands as an alternative for HIV patients, naive or experienced, with pulmonary or extrapulmonary tuberculosis, being a potent antiretroviral with favourable profile concerning tolerability and drug interactions.
Keywords: abdominal tuberculosis, adherence, raltegravir, drug interactions

Introduction

Approximately 8% of all the infections with MTB (Mycobacterium tuberculosis) occur in patients with HIV, making it the most important opportunistic infection worldwide [1,2,3]. Tuberculosis can occur at any stage of HIV infection, regardless of the number of circulating CD4 lymphocytes. However, the incidence of disseminated tuberculosis is higher in patients with advanced immunodepression, being the main cause of death in HIV-infected patients worldwide [1,2,3]. The diagnosis of tuberculosis for coinfected patients is similar to that performed for seronegative patients, but special attention is required for the interpretation of results, due to atypical changes present in patients with advanced immunosuppression:

- Bacteriological examination: smear and microscopy, culture, identification and drug-sensitive assays for MTB [1]
- Imaging: chest X-ray, CT-scan, MRI [1]
- Tuberculin skin test [1]
- In vitro evaluation of gamma interferon produced by activated T lymphocytes in response to MTB specific antigens. There is a wide range of commercially available tests such as Quantiferon TB Gold, T-Spot. TB [1]
- Histological examination which shows specific granulomatous inflammation. In advanced stages of immunodepression there is no specific granuloma [1]

HIV-TB coinfected patients are difficult to manage for various reasons: drug interactions, adverse events due to antiretroviral therapy and TB medication, adherence related issues. Concerning drug interactions, there are many pharmacological interactions between antiretroviral therapy (ART) and antituberculosis drugs, because they are metabolized in the liver by the same enzyme system (cytochrome P450-3A), especially Rifampicin

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(strong enzyme inductor) and protease inhibitors (PIs). Many of the adverse effects of anti-TB drugs (liver toxicity, CNS and gastrointestinal side effects) are similar to ART. So, simultaneous use of these therapies may be associated with additive risk of serious adverse effects.

Case presentation

We would like to present the case of a 44-year old man, who was admitted to our hospital as patient transferred from the Oncological Institute of Bucharest (IOB) diagnosed with abdominal tuberculosis (peritoneal and lymph nodes involvement). The anamnesis revealed two months of fever, abdominal and right leg pain as well as weight loss (15-20 kg). The patient had been initially hospitalized in IOB with a suspicion of pancreatic tumor according to the imaging examination (ultrasound and abdominal CT-scan). Surgery was performed and revealed hepatosplenomegaly, multiple abdominal lymphadenopathies and moderate ascitic fluid. Lymph node and peritoneal biopsy showed chronic granulomatous inflammation without visualisation of AFB on Ziehl-Neelsen smear.

Results

At the admission in our clinic the patient had a good clinical status, with fever (38°C), pale, without peripheral lymphadenopathies, no pulmonary rales, with white plaques on tongue mucosa, a diffuse tenderness on abdominal palpation, hepatosplenomegaly, without neck stiffness.

Laboratory parameters showed moderate normochromic normocytic anemia (Hb 9.9 g/dl), inflammatory syndrome with: ESR 74 mm/1h, RCP 123 mg/dl, hypoalbuminemia (Alb 2.2 g/dl), a positive Quantiferon TB Gold: 13.9 (normal value <0.35), positive HIV serology (on 2 different ELISA methods and Western Blot). The CD_4 level at the moment of diagnosis was 226/mmc and the viral load was 251.793 c/ml (5.2 log10). The resistance testing showed a wild type virus and genetic test for HLA B *5701 was negative. The screening for coinfection: a negative HBsAg, positive HBc-IgG, negative serology for HCV, negative VDRL and TPHA, negative serology for Toxoplasma gondii, a positive IgG for CMV with undetectable DNA-CMV.

Bacteriological and imaging examination showed Candida albicans (sensitive to Fluconazole) on tongue swab, a normal chest X-ray, hepatosplenomegaly, lymphadenopathies and ascites on abdominal MRI and deep venous thrombosis with right tibial vein involvement on Doppler ultrasound examination. Subsequent test for procoagulant status (lupus anticoagulant, anticardiolipin antibodies, S, C protein, antithrombin III, V Leyden factor and serum viscosity) were negative. The anamnesis established that the sexual behaviour (heterosexual) was the risk factor for HIV infection.

Based on physical examination and laboratory parameters, the final diagnosis was HIV infection, clinical and immunological stage C2 (according to the CDC classification of HIV infection) with abdominal tuberculosis as AIDS defining disease, oral candidiasis and deep venous thrombosis (tibial vein).

We initiated tuberculostatic treatment: isoniazid (HIN), Rifampicin (RFP), Pyrazinamide (PZM) and Ethambutol (ETB) well tolerated by our patient, but subsequently he developed digestive adverse reactions strictly related to the administration of ETB, later replaced by Ciprofloxacin. The decision to replace a first-line anti-TB drug (Ethambutol) with a single second-line anti-TB drug, Ciprofloxacin respectively, was based on digestive intolerance appearance and not development of resistance. Antifungal therapy (Fluconazole - 150 mg daily) and anticoagulant (low molecular weight heparin) were added to the TB treatment.

The clinical outcome was favorable with fever remission and decrease of ascitic fluid. According to the 2009 EACS guidelines (European AIDS Clinical Society) on the initiation of HAART in patients with coinfection HIV/TB, it is advisable to start HAART as soon as possible when CD4 level is between 100-350/mmc. However, antiretroviral therapy may be delayed until after completing 2 months of TB treatment especially when there are difficulties with drug interactions, adherence and toxicities. Thus, after two weeks we started antiretroviral therapy (ARV) with Zidovudine (ZDV), Lamivudine (3TC) and Efavirenz (EFV). Because PIs are metabolized by the liver via the cytochrome P450 system, concomitant therapy with Rifampicin (RMP) causes a significant decrease in serum levels of PI drugs with risk of treatment failure and resistance developing. For this reason concomitant therapy with PIs and RMP is generally not recommended, the combination of two nucleos(t) ide reverse transcriptase inhibitors (NRTIs) with EFV being indicated. We recorded a rapid growth of CD_4 to 296/mmc, with immune reconstitution syndrome (IRIS) consisting of fever, abdominal pain and an increase in ascitic fluid. Corticotherapy had to be associated. In the next two weeks, the patient developed severe neuropsychiatric events (hallucinations, nightmares, dizziness, headache) most likely induced by EFV, and ARV therapy was thus ceased. Four months after the tuberculostatic treatment was commenced, with a relatively favorable evolution (the decrease in number and size of abdominal lymph nodes, the disappearance of ascitic fluid) a new viro-immunological evaluation was performed,

with CD_4 211/mmc and HIV RNA 5.9 log 10 c/ml. ARV therapy was resumed with Abacavir (ABV), 3TC and Raltegravir (RAL) in double dose (800 mg every 12 hours, according to the manufacturer's recommendations for co-administration with RMP) with good tolerance and rapid immunological and virological response; a month later the CD_4 level reached 446/mmc and HIV RNA <150 c/ml. The IRIS appeared again with clinical worsening (fever, increase in size of abdominal lymph nodes, reappearance of ascitic fluid) and corticosteroid therapy was restarted.

After 6 months of ARV therapy, the last evaluation showed undetectable viral load and a CD_4 of 496/mmc; the abdominal lymphadenopathies are persistent, with no ascitic fluid.

Discussions

There are few data about the combination of RMP and some antiretroviral agents such as Raltegravir. RMP also induces the enzyme UGT1A1 (Uridin Glucuronil Transferase), leading to increased glucuronidation and reduced plasma levels of Raltegravir. For this reason, it is necessary to use double dose of Raltegravir when it is used in combination with RMP. We stress on the persistence of clinical manifestation associated with MTB infection after 11 months of therapy despite a favorable immunological and virological response. The histological samples were rechecked in another laboratory and the result was similar to the first one. We introduce into the discussion a possible multidrug resistant TB (MDR-TB), low adherence to TB medication and/or the presence of a chronic IRIS with persistence of inflammatory phenomena through restoration of Th1 response. A rather wide range of immune restoration sequences were recorded, worsening the clinical status and thus requiring a long term corticosteroid therapy (at relatively high doses). This decision was made with the known risk of lowering the CD4 level. Despite the fact that IRIS can lead to a paradoxical exacerbation of the clinical status, a diagnosis of TB should not prevent ART introduction in patients with advanced HIV infection. IRIS has been reported to occur in 25-60% of severely immunosuppressed patients in the first three months of ART treatment and it has been associated with a rapid immunologic and virologic response to ART [4]. The psychological impact of clinical relapses due to IRIS was major. In order to maintain the TB and ARV therapy, the patient underwent repeated counseling.

Conclusions

In conclusion, the tuberculostatic treatment always has priority over the ARV therapy which could be postponed, depending on the immunological status and the tolerability of the treatment. Adherence, tolerability and drug interactions are the main causes for the clinical failure in HIV-TB coinfected patients. The most important factor of therapeutic success in HIV-TB coinfection has been the utter adherence throughout the therapy, in case of low compliance the therapeutic risk and the emergence of MDR-BK strains being high. Therefore, Raltegravir stands as an alternative for HIV patients, naïve or experienced, with pulmonary or extrapulmonary tuberculosis, being a potent antiretroviral drug with favorable profile concerning tolerability and drug interactions.

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