



LATE PRESENTER HIV POSITIVE PATIENT WITH SYSTEMIC CRYPTOCOCCAL INFECTION – CASE REVIEW

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Abstract. Introduction. Late presenter HIV positive patients are characterized by low CD4+ lymphocyte count (below 350/mm³) at the moment of diagnosis, frequently having severe opportunistic infections associated. The aim of this study is to present the case of a patient recently diagnosed with HIV infection, with disseminated cryptococcal infection, cryptococcal meningitis and pneumonia. **Methods.** We studied the case of a 21 years old male patient, admitted for asthenia, fever, cough, dyspnea, thoracic pain, myalgias, arthralgias, headache, dizziness, vomiting, altered condition, with the impossibility of maintaining orthostatism, low body weight, oral thrush, and meningeal syndrome. **Results.** Following the paraclinical tests performed the diagnosis of HIV infection was established, with a CD4+ lymphocyte count of 7/mm³. *Cryptococcus neoformans* was cultivated from the blood and cerebrospinal fluid, and the chest x-ray revealed a bilateral bronchopneumonia. The outcome was favourable with Fluconazole monotherapy. Difficulties were encountered with the introduction of antiretroviral therapy due to the appearance of severe side effects to several drugs, and adherence problems, however, undetectable viral load was achieved. **Conclusions.** The management of late presenter HIV positive patient is challenging because of impaired immunity, associated opportunistic infections, and oncoming adherence problems. Widening of HIV testing to a larger area might conduct to a reduction in the number of late presenters, who require a complex therapy, high costs, and have poor prognosis.

Keywords: adherence, adverse effects, fluconazole, HIV, *Cryptococcus neoformans*

Introduction

Late presenter HIV positive patients are defined as those with low CD4+ T-cell counts and/or AIDS defining illness at the moment of discovery of their HIV status. This definition differs slightly regarding the number of CD4+ T-cell count according to different studies, the threshold being 200 cells/mm³ [1], or 350 cells/mm³ (according to the new European definition), patients with CD4+ T-cell counts below 200 cells/mm³ being considered very late presenters. [2,3,4] These patients have a higher mortality rate and a greater HIV-associated morbidity than non-late-presenters. Opportunistic infections are frequent in these patients, conducting to the occurrence of immune reconstitution inflammatory syndrome (IRIS) after the start of antiretroviral therapy, possible drug-drug interactions, drug toxicity, high

pill burden, which might impair patient adherence, thus worsening treatment outcomes. The initiation of antiretroviral therapy should be done early after starting to treat the opportunistic infection (in 2-8 weeks). Regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are recommended as well at this category of patients. It is important to take into consideration the degree of central nervous system (CNS) penetration of the antiretrovirals, especially in patients with signs of CNS disease. With the maintenance of viral suppression the prognosis of these patients improves. [1,3] The risk of HIV transmission is high in late presenters, because the possibility to prevent transmission by complete viral suppression through antiretroviral therapy is lost. [4] The medical costs and the rate of hospital admissions are high in late presenters. Early detection and treatment of HIV infection would be beneficial for the individual, for the society and would reduce the costs on long term, also. [2,4]

Case presentation

We present the case of a 21 years old male pa-

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tient, admitted to our hospital in April 2010, in the 21st day of disease for fatigue, fever, cough, thoracic pain, dyspnoea, headache, dizziness and vomiting, having deeply altered condition, oral thrush, meningeal signs and a slight monoparesis of the right lower limb. Before the start of current disease this patient was performing important physical activity at his workplace. His personal history did not reveal any major diseases in the past, with the exception of repeated parenteral treatments during the year 2000. The patient denied any risk factors for sexually transmitted diseases, presumably being a member of the Romanian cohort of nosocomially infected HIV positive patients. The suspicion of HIV infection was confirmed by the laboratory findings, the patient having two ELISA and one Western Blot tests positive. The CD4+ T-cell count was 7 cells/mm³, the leucocyte count was 2700 cells/mm³, with 75.7% neutrophils, 22.6% lymphocytes, the triglyceride level was 207 mg/dl, and total cholesterol level was 219 mg/dl. Tests for hepatitis B and C viruses and mycobacterium tuberculosis were negative. The body mass index (BMI) of the patient was 19.95, the Karnofsky score regarding the quality of life 20%. The Karnofsky score was established according to The Sanford Guide to HIV/AIDS Therapy 2009, the value of 20% meaning a very sick person, who needed hospital admission and active supportive treatment. [5] The patient had slight papilledema and the cerebral computer tomography (CT) scan revealed slight diffuse biemispheric oedema. (Figure 1.) Lumbar puncture was performed and the cerebrospinal fluid (CSF) analysis revealed clear liquor, with Pandy +/-, 7 cells / μ l, glucose 59 mg/dl, proteins 38 mg/dl, chloride 118 mEq/l, lactic acid 23.9 mg/dl. On the Gram stained smear cryptococcal cells were observed, the latexagglutination was positive for cryptococcus spp., the CSF culture revealed *Cryptococcus neoformans*, sensitive to Fluocytosine (MIC - minimum inhibitory concentration ≤ 1), Fluconazole (MIC 2) and Amphotericin B (MIC ≤ 0.25). Blood culture revealed *Cryptococcus neoformans* also, with the same sensitivity to antifungal agents. The chest X-ray showed diffuse basal bilateral infiltrates. (Figure 2.) After these findings the diagnosis of advanced HIV infection (late presenter patient), systemic infection with *Cryptococcus neoformans*, cryptococcal meningoencephalitis and pneumonia was established. Fluconazole monotherapy was introduced in a dose of 400 mg bid intravenously for 8 weeks, followed by 400 mg qd given orally for another 4 weeks, followed by 200 mg qd orally as maintenance therapy. After 4 weeks of sustained antifungal therapy antiretrovirals were introduced. We chose a regimen with good cerebral penetration: zidovudine, lamivudine and lopinavir/ritonavir (CNS penetration effectiveness

- CPE – score according to Letendre et al.: $1+0.5+1 = 2.5$). [6] However this regimen was not tolerated, severe gastrointestinal adverse effects appeared due to lopinavir, mimicking an acute abdomen. Therefore lopinavir was exchanged with efavirenz (CPE score 0.5). After 6 weeks of antifungal therapy the CSF culture, smear and latexagglutination were still positive for *Cryptococcus neoformans*. The CD4+ T-cell count showed a slight increase (29/mm³) after 4 weeks of antiretroviral therapy. The patient was released from hospital with orally administered fluconazole. He returned after 2 weeks because of severe rash and anemia (hemoglobin 5.2 g/dl). The antiretroviral regimen was exchanged again due to the adverse effects, lamivudine with abacavir and nevirapine (CPE score: $0.5+1+1 = 2.5$) was started. After 14 weeks of antiretroviral therapy HIV viral load could be determined (6150 copies/ml) and CD4+ T-cell count was repeated (56/mm³). At this moment BMI was 21.8, the Karnofsky score 90%, showing that the patient was able to carry on normal activity, with minor signs or symptoms of disease. The EuroSIDA risk score was 2.16, calculated according to Mocroft A, Lederberger B, Zilmer K et al. [7] This score was interpreted as the chance of appearance of new AIDS events or death within 3 months of 1 in 276, within 6 months of 1 in 138 and within 12 months of 1 in 69. In 8 months from the start of antifungal therapy CSF analysis was repeated, showing negative cultures, negative smear, with a persistence of positive latexagglutination for *cryptococcus* spp. However, the CD4+ T-lymphocyte count was 23 cells/mm³, therefore it was repeated in two weeks (47 cells/mm³) together with the HIV viral load (7087 copies/ml). The EuroSIDA risk score was 2.98, showing the same risk rates as mentioned above. Adherence problems were suspected, and confirmed. The patient was counseled, and a PI containing regimen was introduced with boosted fosamprenavir, abacavir and lamivudine (CPE score $1+1+0.5 = 2.5$). In 18 weeks following the start of this regimen and 50 weeks from the start of antiretroviral therapy undetectable viral load was obtained. In 18 months from the first admission the BMI was 20.32, the CD4+ T-cell count was 42/mm³, Karnofsky score 80% and the EuroSIDA risk score increased to 3.19 suggesting adherence problems again. The Karnofsky score of 80% showed the patient's ability to perform normal activity with effort, with some signs and symptoms of the disease. The patient willingly interrupted the secondary prophylaxis with fluconazole, had a slight headache, but refused lumbar puncture. The EuroSIDA risk score was 3.19, showing the chance of appearance of new AIDS events or death within 3 months of 1 in 63, within 6 months of 1 in 32 and within 12 months of 1 in 16. The patient had

6 admissions to the hospital in 2010, with a total of 91 days of hospitalization, without any admissions in 2011. Dyslipidaemia was no longer present in 2011 with triglyceride levels of 80 mg/dl, total cholesterol levels of 190 mg/dl.

The cerebral CT scan showed slight diffuse biemispheric oedema.



Figure 1. Cerebral computer tomography

Diffuse basal bilateral infiltrates were observed on the chest X-ray



Figure 2. Chest radiograph of the patient at the moment of admission

Discussions

One of the peculiarities of the case presented is that although this patient was a late presenter with very low CD4+ T-lymphocyte count and a severe opportunistic infection at the moment of diagnosis, he had no prior clinical signs that might have suggested the presence of HIV infection. Reliance on clinical findings only to perform HIV testing is inadequate, possibly conducting to the discovery of HIV infection in a very advanced stage, as in this case.[8] Despite the initial signs of severity of the disseminated cryptococcal disease, with the pres-

ence of signs of high intracranial pressure (headache, vomiting, papilledema, diffuse biemispheric oedema on the cerebral CT scan), the presence of monoparesis of the right lower limb, cryptococcal pneumonia associated with dyspnoea, and the positive blood culture, appointing to a poor prognosis, the outcome was favorable with fluconazole monotherapy. Although bitherapy with a combination between amphotericin B, flucytosine or fluconazole, or even tritherapy using these three antifungals is recommended for induction, this could not be performed in our case because of the lack of amphotericin B and flucytosine, however, the determination of the MIC of the isolated *Cryptococcus neoformans* assured us that it was a fluconazole-sensitive strain, allowing the usage of fluconazole in monotherapy. [9,10] The duration of induction therapy differs according to different guidelines, one of the recommendations being fluconazole 800mg/day given for 2-4 weeks, followed by 400mg/day given for another 8-10 weeks, followed by 200 mg/day as secondary prophylaxis, that must be maintained until the CD4+ T-cell count increases above 200/mm³ for at least 6 months. [11] Another recommendation for fluconazole monotherapy is to maintain a high dose of at least 800 mg/day given orally for at least 10 weeks, followed by the maintenance therapy of 200mg/day, until the level of CD4+ T-cells is maintained above 100 cells /mm³ and the viral load is undetectable for at least 3 months, with at least 12 months of previous antifungal therapy. [9] Our treatment strategy was situated between these two recommendations, with 8 weeks of fluconazole 800mg/day given intravenously, followed by 4 weeks of 400mg/day orally, and then maintenance therapy with 200mg/day orally. The clinical and laboratory findings were favourable with this treatment, with negative CSF culture, the remission of the symptoms of high intracranial pressure, of the right lower limb monoparesis, and of the pulmonary disorders. The cryptococcal antigen persisted in the CSF, however, its presence is not necessarily correlated with the outcome of cryptococcal meningitis, and it is not considered a tool in conducting the antifungal therapy. Thus other authors consider it necessary to continue the maintenance therapy until the cryptococcal antigen is present in the CSF. [10,12] In our case maintenance therapy was necessary due to the persistent low level of CD4+ T-cell count.

The suggested moment of start of the antiretrovirals is after 2-8 weeks of antifungal therapy, although another study suggests that it should be postponed until 10 weeks of antifungal therapy have passed. [1,3] In our case, antiretrovirals were introduced after 4 weeks of fluconazole monotherapy. In the choice of antiretroviral therapy many aspects were considered: the recommendation of the guidelines

for naive late presenters, the cerebral penetration effectiveness score of the drugs, the possible interactions. Drug toxicity and side effects were an important issue also, encountering several adverse effects at this patient. The initial choice was boosted lopinavir associated with zidovudine and lamivudine. Although the combination of zidovudine with lamivudine is no longer recommended as first line therapy in the naive patient it was chosen due to its availability and the high CPE score and CNS penetration effectiveness rank much above average [4] for zidovudine. Although the patient had high triglyceride and cholesterol levels, which could have been worsened by the usage of lopinavir, we opted for this drug because of its high cerebral penetration. However lopinavir had to be stopped early, due to its severe gastrointestinal side effects. It was replaced with another drug used in the first line therapy of late presenter naive patients, efavirenz. Although with a lower CPE score than boosted lopinavir, it was chosen because of no interactions with fluconazole. However, its administration had to be discontinued also, due to a severe rash. The concentration of zidovudine is elevated by fluconazole, this was probably the reason of the appearance of another important side effect, severe anemia. Zidovudine had to be replaced with abacavir, with the same CPE score of 1, but a lower CNS penetration effectiveness rank (above average - 3). Efavirenz was replaced with another NNRTI, nevirapine, with a higher CPE score, but potential interactions with fluconazole. This regimen was well tolerated; however the appearance of adherence problems jeopardized its usage. Therefore nevirapine was exchanged with a PI, a drug with a much higher genetic barrier and good tolerability, boosted fosamprenavir. Undetectable viral load was achieved with this regimen containing boosted fosamprenavir, abacavir and lamivudine. The usage of boosted fosamprenavir could have conducted to the worsening of dyslipidaemia, but this did not happen in the case presented. [6,13] Despite the low baseline CD4+ T-cell count the patient did not have IRIS, although it appears in 30% of the cases. [10] This could be explained by the lack of rapid increase of the CD4+ T-lymphocyte count at this patient. The outcome of the patient was initially favourable, with a much improved performance status, an increase in the body mass index, a good quality of life, apparent health, with negative CSF culture and undetectable viral load, no hospitalization, and consequently lower costs during the year 2011. The patient continued the antiretroviral, the secondary prophylactic antifungal therapy, and the prophylaxis for pneumocystosis. Possibly due to high pill burden and the apparent good health adherence problems re-emerged, worsening the

EuroSIDA risk score and the prognosis of the patient. Solving the adherence problems will be the key element in the future management of this patient.

Conclusions

The management of late presenter HIV positive patients is complicated due to the associated opportunistic infections that appear at a profound immunodepression. Systemic cryptococcal infection at the patient with advanced HIV infection has poor prognosis, however with possible favourable outcome in case of appropriate antifungal and antiretroviral therapy. Poor adherence worsens the prognosis of these patients, who become difficult to manage. By extending the HIV testing to a larger area the number of late presenter patients could be reduced, thus lowering the number of patients with severe opportunistic infections, who demand complex management, high costs and have poor prognosis.

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