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Combined Treatment with Tenofovir ($C_9H_{14}N_5O_4P$), Emtricitabine ($C_8H_{10}FN_3O_3S$) and Efavirenz ($C_{14}H_9ClF_3NO_2$) in Multiple Spleen Abscesses with Bacterial and Fungal Etiology in HIV Infected Patients

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Abstract. *Patients with human immunodeficiency virus (HIV) infection represent a risk group for developing spleen abscesses. The paper presents a short review and case illustration, describing the characteristics and underling treatment of HIV-infected patients with infectious comorbidities. There are few reports in literature of multiple spleen abscesses with double, microbial and fungal etiology in HIV-infected patients. A 35 years old male patient was referred to the Infectious Diseases Clinic with prolonged fever. In the last 2 years he had worked as a waiter and had multiple unprotected sexual contacts. The physical examination showed: fever, tongue and pharynx with Candida albicans deposits, enlarged cervical, submandibular, axillar, inguinal lymph nodes and splenomegaly. Biological tests including HIV antibodies (Ab) ELISA, CD4, HIV Western blot test, cultures and paraclinical investigations-abdominal ultrasonography and computed tomography were performed. There was a significant inflammatory response, HIV Ab were positive, CD4 cells=17/µL and Western blot HIV test was positive. Abdominal ultrasonography showed: splenomegaly with 3 hypoechogenic round images (13-17mm) at the superior pole, in the hilum and inferior pole. HIV infection stage C3 with oropharyngeal candidiasis and multiple splenic abscesses were diagnosed. After 6 weeks of antibiotic and antifungal therapy total splenectomy was performed. The cultures from splenic abscess contents revealed Acinetobacter baumannii and Cryptococcus neoformans. Under appropriate antibiotic and antifungal treatment, the postoperatory evolution was favorable.*

Keywords*: antibiotic, antifungal therapy, spleen abscesses.*

1. Introduction

Spleen abscesses are rare clinical entities, having a frequency between 0.05 and 0.7% [1]. Infectious outbreaks in the body are the main risk factor, splenic abscesses being reported in patients with endocarditis, osteomyelitis, pneumonia, mastoiditis and abdominal infections [2]. Other risk groups are immunocompromised subjects: human immunodeficiency virus (HIV) infected patients, immunosuppressive therapy, intravenous (i.v.) drug users [3]. Because the symptoms are non-specific and the medical history and physical examination are not sufficient for diagnosis, the splenic abscess remains a challenge for physicians.

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Modern imagistic methods, abdominal ultrasonography (US) and computed tomography (CT) scan facilitate an early diagnosis of splenic abscess [4]. The literature shows that the specific mortality is up to 47% and, without antibiotic treatment, it may increase to 100% [2]. The current management, which is based on early imagistic diagnosis, antibiotic therapy and surgical treatment, decreases the rate of mortality to less than 10% [4].

2. Materials and methods

The paper presents a comprehensive review regarding rare infectious comorbidities in HIV infected patients and treatment specifications, followed by an illustrative report.

Chronic HIV infection is associated with a number of co-infections that are associated with immune activation at various stages, especially after antiretroviral therapy initiation in the form of Immune Reconstitution Inflammatory Syndrome (IRIS) [5].

The role of T cells in IRIS was proven with evidence of more pronounced effector activity in IRIS patients that may conduct to exacerbated tissue pathology. Recent researches highlighted the role of myeloid cells in IRIS alongside the involvement of antigen load in the syndrome. Furthermore, there have been published preliminary reports suggesting the involvement of inflammasome occurrence in IRIS [5]., The importance of activated immune T and myeloid cells besides biomarkers in cryptococcal IRIS were assessed in detailed at the site of infection [5].

Despite concrete evidence that HIV infection should be treated upon diagnosis even at CD4 T cell counts above 500 cells/μL [6], the sobering reality is that many patients present late at diagnosis or treatment initiation in both resource limited and resource rich settings [7].

Deepening the details regarding the connections between opportunistic infections at the moment of antiretroviral therapy initiation and IRIS pathogenesis will improve the protocol for prevention and treatment. Remote IRIS sequelae have not been fully elucidated. Chronic comorbidities as contamination with hepatitis C virus or herpesviruses have a major role in maintaining immune activation in HIV patients under chronic treatment [5].

Anti-retroviral therapy increased life expectancy in HIV-infected patients. Consequently, HIV patients are exposed to diseases characteristic of old age [8]. According to Zingmond [8] the rate of chronic cardiovascular or renal diseases increased among patients diagnosed with HIV. By default, the price of treatment including the management of associated diseases has increased.

The majorities of these comorbidities are based on an inadequate lifestyle (hypertension, diabetes, chronic liver or kidney disease). Improving nutrition and lifestyle as well as primary prophylaxis in outpatient clinics could reduce the costs associated with these conditions [8].

Despite the benefit of implementing combination antiviral therapy, 1.5 million HIV-infected patients have died in 2010 [9]. The immune deficiency induced by HIV multiplies the risk of coinfections with pathogens conditioned by the cellular and innate immune response and several infections conditioned by the phagocytic action of the host.

Moreover, administration of combined antiretroviral therapy in HIV patients with associated infectious conditions does not always have the expected results [10]. According to Chang and al [10] the most prevalent pathogens involved in occurrence of infectious comorbidities in HIV patients worldwide are hepatitis C virus (HCV), hepatitis B virus (HBV), Cryptococcus neoformans, Plasmodium falciparum and Mycobacterium tuberculosis.

The World Health Organization (WHO) reports indicate that there are 14 million patients worldwide with coinfection HIV and Mycobacterium tuberculosis and tuberculosis is the most frequent opportunistic infection found in patients diagnosed with HIV. The association of pulmonary tuberculosis was responsible for 26% of deaths in patients with acquired immunodeficiency (AIDS). Data published by the WHO in 2010 showed that 39% of all new cases of Mycobacterium tuberculosis infection occurred in HIV-infected patients [11].

Infectious comorbidities in immunocompromised patients are common. But in the literature there are few informations regarding management of combined infections between different bacterial, fungal

species and Mycobacterium tuberculosis in HIV positive patients. Patients with HIV are more prone to develop mycobacterium infections. The most affected organs with Mycobacterium fortuitum infections in susceptible individuals with AIDS are the lungs, lymph nodes, or the skin and also disseminated form of disease may occur. Soto Arquinigo and collaborators [12] described a patient diagnosed with HIV receiving antiretroviral therapy that associated hepatosplenomegaly and abdominal tomography showed splenic nodular lesions. The splenic culture was positive for Mycobacterium fortuitum, with additional positive polymerase chain reaction (PCR) to Mycobacterium tuberculosis. The standard treatment protocols for this type of infection should be based on the proven susceptibility from the cultures performed [12].

Heller and collaborators described the data from 82 patients diagnosed with HIV and abdominal tuberculosis which have been examined by ultrasonography [13]. The reports were assessed and compared with chest radiography. The results showed enlarged abdominal lymph nodes in 75.6% of the cases, splenic abscesses in 41.2% and liver lesions in 30.6%. Chest radiography depicted miliary infiltrations in 21.9% of the patients; 26.8% of the patients didn't present typical radiological lesions for pulmonary tuberculosis. In HIV patients with this profile it is recommended to perform abdominal ultrasonography to improve the diagnosis of HIV-associated extra-pulmonary tuberculosis [13].

In pediatric and adult patients with HIV infection and in uninfected children and adults, the management of severe bacterial infections are similar. It is always indicated to collect samples for microbiological examination before starting the treatment [14]. Yet, in cases with severe bacterial infections it is recommended to promptly start empirical administration of antibiotics, without waiting for the antibiogram results. The treatment may be adjusted later according to culture results. The regional rate of antibiotic resistance of common pathogens (as penicillin-resistant Streptococus pneumoniae) and the previous use of other antibiotics are very important aspects to asses before starting empiric therapy. After the pathogen is identified, antibiotic susceptibility should be analyzed and proper antibiotic therapy should be implemented [14].

We present the case of a patient diagnosed with HIV infection and multiple splenic abscesses with microbial and fungal etiology, successfully treated. A 35-years-old male patient was addressed by the general practitioner to the Clinic of Infectious Diseases, due to a prolonged febrile syndrome. On admission, the patient was febrile, asthenic, presenting dysphagia and marked weight loss (15 kg in 2 months). From the medical history we noted that the patient had 2 episodes of chest shingles (thoracic zona zoster) in the last 2 years. He had worked as a waiter in Italy and had multiple unprotected sexual contacts during this period.

The onset of the disease was insidious, with progressive fatigue, loss of appetite, weight loss. For almost 3 weeks before hospitalization he presented persistent fever, accompanied by a pustular rash initially localized on the thorax, abdomen and limbs, that afterwards became generalized. He was unsuccesfully treated with antipyretics and penicillin by the family physician, so he was addressed to the Infectious Diseases Clinic for further investigations.

The physical examination on admission showed altered status, body mass index =18.24 kg/m2, pallor and generalized pustular rash. The tongue and the pharynx were coated with whitish adherent deposits. There were enlarged, mobile, painless lymphnodes in the cervical/submandibular/axillary and inguinal regions. The spleen was enlarged and painful. No other changes were observed.

The laboratory tests indicated leukopenia with neutrophilia, mild anemia and inflammatory status. The glycemia, renal, liver and pancreatic tests were normal. Hepatitis B and C serology and Treponema Pallidum Hemagglutinations Assay(TPHA) were negative. Urine and blood cultures were sterile. Chest radiography was normal. The lumbar puncture was performed. The biochemical tests of the cerebrospinal fluid (CSF) were normal. The CSF cultures for microbial flora, including Mycobacterium tuberculosis and fungal infections were negative. The culture for M. Tuberculosis from the respiratory secretions collected from the broncho-alveolar lavage was negative. The pharyngeal and tongue swab indicated C. albicans infection. HIV Ab were positive, CD4 cells level was 17/µL, the Western blot HIV test was positive and the HIV viral load was 191 547 copies/ml.

The abdominal US showed normal aspect, except splenomegaly with 3 hypoechoic round splenic images at the superior pole, hilum and inferior pole. The contrast-enhanced abdominal CT confirmed 3 round, hypodense, noniodofile splenic lesions, varing between 16-19mm (Figure 1).

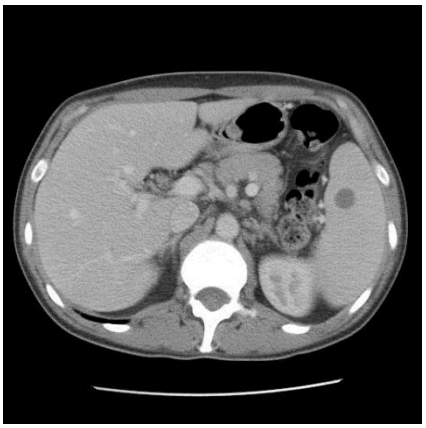

Figure 1. The contrast-enhanced CT shows a round image situated in the superior pole of the spleen, hypocaptant in the venous time

Corroborating data, we established the diagnosis of HIV infection stage C3, oropharyngeal candidiasis and multiple splenic abscesses.

Medical treatment was started using piperacillin-tazobactam (Tazocin), fluconazole, paracetamol, ibuprofen and omeprazole. Following this treatment, the patient continued to be feverish, but the rash and the oropharyngeal candidiasis were alleviated. After 3 weeks Tazocin was replaced with Meropenem associated with Vancomycin for another 3 weeks. After 6 weeks of therapy with broad spectrum antibiotics, the patient continued to be feverish. Following the surgical consultation, with the patient's consent it was decided to perform a surgical intervention for splenectomy. Intraoperatory, the surgeon observed an enlarged spleen with multiple abscesses. The surgeon performed the splenectomy in the hilum, with the ligature of the splenic artery and the drainage of the spleen lodge. Cultures were taken from the contents of the abscess for microbial and fungal cultures. The post-operatory evolution was favorable.

After surgery, the patient continued the prophylactic post-operative treatment with Ciprofloxacin and Fluconazole for 10 days. The laboratory tests performed 7 days after surgery were normal and the blood culture was sterile. The cultures from the spleen abscesses content revealed C. neoformans and A. baumannii, confirming the bacterial and fungal etiology of these abscesses. The patient became afebrile and regained appetite and the antiretroviral therapy was started with Tenofovir, Emtricitabine and Efavirenz for immunological recovery. He was discharged with recommended periodic follow-up.

Some chemical features regarding the antiretroviral drugs:

TENOFOVIR

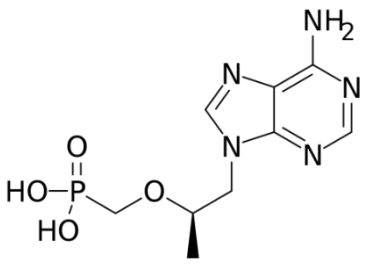

Figure 2. Chemical formulae for Tenofovir

Tenofovir disoproxil is a nucleotide analog reverse-transcriptase inhibitor (NtRTI) [15]. Its action is based on selective inhibition of viral reverse transcriptase, an important enzyme of retroviruses. On the other hand, this drug performs low inhibition of human enzymes, as DNA polymerases α, β, and mitochondrial DNA polymerase γ [16]. Tenofovir induces premature completion of DNA transcription, inhibiting viral multiplication [15]. It's chemical formula is C9H14N5O4P, with a molar mass of 287.213 g/mol g·mol−1

EMTRICITABINE

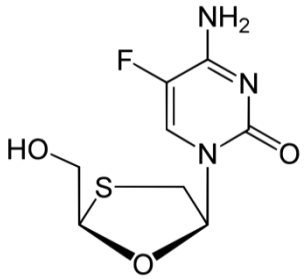

Figure 3. Chemical formulae for Emtricitabine

Emtricitabine is a cytidine analogue. Its main action is based on reverse transcriptase inhibition, canceling the action of the enzyme responsible of HIV RNA copying into new particle DNA. [17] Disrupting the central mechanism of HIV replication, emtricitabine decreases the viral load and improves the function of immune cells (CD4 positive T lymphocytes) [17]. It's chemical formula is C8H10FN3O3S, with a molar mass of 247.248 g/mol g·mol−1

EFAVIRENZ

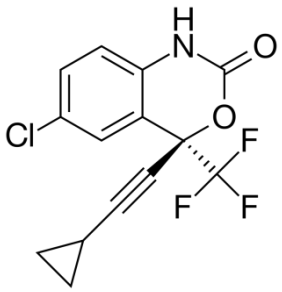

Figure 4. Chemical formulae for Efavirenz

Efavirenz belongs to the NNRTI class of antiretrovirals. The reverse transcriptase is the most important viral enzyme, which promote the transcription of viral RNA into DNA. Nucleoside as well as non-nucleoside RTIs inhibit this crucial enzyme. Nucleoside RTIs, bind at the enzyme's active site. NNRTIs have a different mechanism of action. These drugs bind to a distinct site named the NNRTI pocket [18]. Efavirenz does not act against HIV-2 because HIV-2 reverse transcriptase pocket presents a different structure. This fact represents the base of NNRTI class resistance. [18] Efavirenz's chemical formula is (S)-6-chloro-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one; C14H9ClF3NO2. Its molecular mass is 315.68 g/mol [18].

3. Results and discussions

In the era of antibiotics that contributed to the decreasing of the infectious outbreaks, the spleen abscesses have become rare clinical entities. In immunosuppressed patients, splenic abscesses should be differentiated from lymphomas, metastases, infarctions or hematomas that may have similar imagistic characteristics [19]. Total splenectomy remains the standard care for splenic abscesses, this procedure being applied in most surgical centers. The method removes both the organ and the septic source. Other minimally invasive methods, that are shortening the length of hospitalization, include laparoscopic splenectomy and imagistic-guided percutaneous drainage. [20] Splenectomy is preferred in cases with multiple splenic abscesses, while imagistic guided percutaneous drainage is performed in cases with a single abscess.

Recent researches described infections incidence after splenectomy of 14.3% [21] and the mortality rate 0.3% [22]. In patients with untreated splenic abscess, the mortality reaches 100%. Prophylactic administration of pneumococcal vaccine or polymicrobial vaccine would reduce the infection and mortality rates. Some studies indicated that most of the infections occur in the first 2 years following splenectomy [23]. Blood cultures from peripheral venous blood or abscess cultures content allow the isolation of aerobic or anaerobic germs in automated BACTEC systems. In our case, total splenectomy was performed and cultures were made from the abscesses content obtained during the surgical procedure. The identification of A. baumannii was made with automated method Witek-2 Compact. C. neoformans was identified using Sabouraud culture medium with automated method from Witek-2 Compact. The cultures made using Lowenstein-Jensen medium in order to detect M. tuberculosis were negative.

Although we have given broad-spectrum antibiotics for 6 weeks, the patient continued to be febrile and malaise. After radical surgery (total splenectomy), the patient became afebrile and its general condition has improved. As the patient is immunocompromised, an important objective is the prophylaxis of the infections, so the patient must be immunized against Streptococcus pneumoniae, Meningococcus and Haemophilus influenzae type B using available vaccines. In order to prevent any fungal infections the patient will continue a long-term treatment with fluconazole, 200 mg/day, orally.

To our knowledge this is the first case reported with multiple splenic abscesses in a patient with acquired immune deficiency syndrome and dual etiology, microbial (A. baumannii) and fungal (C. neoformans), who underwent total splenectomy. We highlight that the postoperative evolution of the patient one month after discharge was favorable, with no infectious complications.

4. Conclusions

In conclusion, an early diagnosis of splenic abscess in HIV-infected patients remains a substantial challenge for most medical practitioners. Modern imagistic tools facilitate the early detection of splenic abscess. Broad-spectrum antibiotic therapy associated with adequate surgical procedures improve the prognosis of these patients. Post-operative clinical and therapeutic monitoring should ensure the immunological recovery and infections prophylaxis in all splenectomized patients.

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