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Opportunistic Infections in Aids Patients

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Abstract

Individuals infected with human immunodeficiency virus (HIV) often develop multiple complications and comorbidities, among them, opportunistic infections. The highest incidence of opportunistic infections was reported in the group of patients with CD4 lymphocyte levels below 200 cells / mm. Candidiasis, toxoplasmosis and pneumocystis pneumonia (PCP) were the main representatives. Candidiasis and pneumocystosis are fungal infections caused by Candida spp agents and Pneumocystis jirovesi respectively, while toxoplasmosis is caused by Toxoplasma gondii. Candida spp. is present in the oral mucosa of human in a commensal way and when the individual becomes immunosuppressed, it becomes pathogenic. The main manifestation of oropharyngeal candidiasis in HIV-infected individuals is pseudomembranous candidiasis characterized by yellowish-white plates easily removable; esophageal candidiasis presents with dysphagia and chest pain. The diagnosis is predominantly clinical, and oral fluconazole remains the treatment of choice. It is believed that PCP occurs by a reactivation of a latent infection, person to person transmission and even through environmental sources. It is characterized by an insidious onset with progressive dyspnea, fever, nonproductive cough and chest discomfort that gets worse over the weeks. A bronchoscopy with bronchoalveolar lavage is the gold standard diagnosis. The treatment with trimethoprim-sulfamethoxazole is the recommended first line choice, prophylaxis should also be performed with the same drug when CD4 + lymphocytes <200 cells / mm³. Transmission of *T. gondii* occurs by direct ingestion of oocysts, by ingestion of raw or undercooked meat, through blood transfusion, organ transplant or via the placenta. It is believed that the toxoplasmosis in immunocompromised individuals, usually results from reactivation bradyzoites cysts .The symptoms include headache, confusion or altered mental status, fever, lethargy, seizures, among others. Diagnosis is made from clinical, imaging and serology tests. The treatment of choice, a combination of pyrimethamine and sulfadiazine and prophylaxis with trimethoprim and sulfamethoxazole should also be performed when the CD4 + T lymphocytes <200 cells / mm³. Current knowledge about the epidemiology, clinical features and treatment of these diseases is important in the management of patients with HIV and is the focus of this review.

Keywords: Opportunistics Infections, Pneumocystosis, Oral-esophageal Candidiasis, Neurotoxoplasmosis and AIDS

Introduction

The pandemic of human immunodeficiency virus (HIV) is one of the biggest health crises ever faced by mankind. Overall, 34.0 million people were living with HIV at the end of 2011. Sub-Saharan Africa remains the most severely affected, with almost 1 in 20 adults (4.9%) living with HIV [1]. In Brazil between 1980 and 2012672 697 cases of AIDS were recorded [2]. AIDS (acquired immunodeficiency syndrome) appeared epidemically in the 1980's. It is an advanced clinical manifestation of infection with human immunodeficiency virus (HIV), characterized by low lymphocyte count CD4 + below 200 / mm³ [3].

Patients with human immunodeficiency virus (HIV) infection often develop complications and multiple comorbidities, among them opportunistic infection (OI). They must always be considered in symptomatic patients with HIV / AIDS [4]. Before widespread

use of potent combination of the antiretroviral therapy (HAART), opportunistic diseases, which were defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected people, were the leading cause of morbidity and mortality in the population during the natural course of the disease [5]. The relationship between HIV and OIs is based on immunosuppression [6].

From the mid-90s, the widespread use of HAART deeply influenced the reduction of mortality associated with OI in HIV-infected patients, in countries where these therapies are affordable and cheap [5,7]. Despite the HAART era, the OIs continue to cause considerable morbidity and mortality in HIV-infected patients. This is due to three primary reasons: asymptomatic patients seek medical assistance only when an OI becomes an indicator of AIDS; other patients do not make use of HAART for psychosocial and economic factors; and there are still those who do not have a good response to antiretroviral agents due to poor adherence, drug toxicity, drug interactions or unexplained biological factors [8,9]. The highest incidence of opportunistic infections was reported in the group of patients with CD4 lymphocyte levels below 200 cells / mm³ [10]. Studies show that the major co-morbidities associated with AIDS are candidiasis, followed by tuberculosis, pneumocystosis, toxoplasmosis, herpes, Kaposi's sarcoma, cryptococcosis, and infections by protozoa [11].

Therefore, early recognition and proper management of these major OIs by health professionals are strictly necessary to reduce the morbidity and mortality of patients with HIV. Thus, the present literature review aims to address the major diseases in the gastrointestinal tract, respiratory and central nervous system that manifest in patients with AIDS when the CD4 + T lymphocytes are below 200 cells / mm³, which are: candidiasis, pneumocystosis and neurotoxoplasmosis [12,10].

Pneumocystosis

Introduction

The PCP is an opportunistic infection caused by Pneumocystis Jirovesi. Often affects the immunosuppressed, particularly individuals with Acquired Immune Deficiency Syndrome (AIDS) [13]. The etiologic agent rarely produces disease in immunocompetent individuals, but causes severe pneumonia in individuals with a variety of debilitating medical conditions [14]. It is believed that the initial infection with P. jirovecii usually occurs in early childhood; two-thirds of healthy children have antibodies to P. jirovecii between 2 and 4 years of age [15].

Epidemiology

Pneumocystis was originally reported by Carlos Chagas (Brazil) at the beginning of the twentieth century, more precisely in 1909, when he observed the never before identified morphological form in the lung tissue of a guinea pig being used for the study of human american trypanosomiasis, mistaking it as one of the forms present in a stage of Trypanosoma cruzi's life cycle. Soon after, Antonio Carini described similar structures in the lung tissue of mice infected with Trypanosoma lewisi and suspected that the morphological form could be a new microorganism. In 1912, at the Pasteur Institute in Paris, a more detailed study of the content from the Carini investigation was conducted by the couple Delanoë. Thus, it was confirmed that it was a new biological entity, by observing the samples sent by Carini and also by identifying these structures in the lungs of mice without infection with Trypanosoma. This distinct species was designated a Pneumocystis, because it was isolated in the lung, with the specific restrictive carinii, honoring Antonio Carini, who had allowed such an investigation [16-18].

The microorganism was classified then as protozoa until 1980. This opinion was based on the following criteria: 1) strong similarity of the microorganism morphology and pathology in the host; 2) absence of some phenotypic characteristics of fungi; 3) presence of morphological characteristics typical of protozoan; 4) ineffectiveness of antifungal drugs against the agent; 5) effectiveness of drugs commonly used to treat protozoa [19]. Thus, in 1988 by DNA analysis, it was demonstrated that the Pneumocystis is a fungus. After appropriate classification, genetic studies revealed different sequences in different mammals, and was found that Pneumocystis in humans is different from that in other species. Therefore, in 1999, Frenkel proposed changing the name of the organism that causes human infection Pneumocystis jiroveci, named after the Czech parasitologist Otto Jirovec, who described the microorganism in humans [20,21].

P. jirovecii is an opportunistic pathogen, ubiquitous unicellular eukaryote, hard to be cultivated and with specificity restricted to humans. According to their biological characteristics and because of its tropism for the lung, P. jirovecii usually causes severe interstitial pneumonia, known as PCP or Pneumocystis pneumonia (PCP) in the immunocompromised and, as a rule, asymptomatic infection in the immunocompetent [22,23].

This fungus was recognized as a potential infectious agent to humans only in the 30s and 40s of the last century, when he was deemed responsible for several cases of disease and some interstitial pneumonia outbreaks in premature infants and malnourished children, a result of extreme social difficulties due to World War II [24]. It was the most common causative agent of interstitial pneumonia in immunocompromised children by primary causes and also in individuals treated with immunosuppressive drugs after organ transplantation or for the treatment of malignancies, particularly lymphoreticular and the collagenases [25].

Although there was awareness that PCP caused pneumonia in immunocompromised patients, this problem assumed alarming proportions in the 1980s with the emergence of Acquired Immune Deficiency Syndrome. During this period, 70% to 85% of those infected with human immunodeficiency virus (HIV) developed pneumocystosis, being it the primary opportunistic infection found in these individuals [26,27]. The first report related to a potential human immunodeficiency syndrome occurred in 1981, when the Centers for Disease Prevention and Control (CDC) confirmed the first cases of pneumocystis in five young gay men in the city of Los Angeles, raising the possibility of an immune cell dysfunction (still of unknown etiology), which later came to be called AIDS [28]. Since then, considering the epidemiological context that followed, pneumocystosis gained huge importance, becoming

one of the priorities in the epidemiological and clinical perspective related to HIV-infected patients' monitorization [29].

In industrialized countries, due to the widespread use of pneumocytosis prophylaxis, established in the early 90s and to the establishment of Antiretroviral Therapy (HAART) in 1996, patients had an improvement in immunity and a decrease in mortality from this infection [17]. This evolution has resulted in reduced incidence of PCP and increased life expectancy in patients with pneumonia. However, PCP remains an important clinical problem, remaining as a major opportunistic infection that affects individuals infected by HIV [29].High prevalence of the disease is still found in individuals who do not respond to treatment (HAART), in those who do not adhere to the treatment and / or prophylaxis and HIV positive individuals who have not been diagnosed. The incidence is also high in countries where the HIV carriers do not have access to effective antiretroviral treatment [30,31].

The European Surveillance Report on HIV in 2012, of the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) showed that in the European economic space, in 2012, the most common AIDS-defining disease was pneumocystosis, with 25% of cases, followed by esophageal candidiasis with 13% and pulmonary tuberculosis with 10%, thus demonstrating that the PCP remains a cause of significant morbidity and mortality in HIV patients, even after HAART[19].

Pathogenesis

The transmission of pneumocystis pneumonia (PCP) is not completely understood, nor has its environmental niche been fully identified. For decades, the theory of reactivation of latent infection - in which the Pneumocystis remained latent in the body and cause disease when the immune system has failed - was popular. Currently there is evidence that transmission from person to person is the most likely way of getting new infections, although acquisition by environmental sources can also occur [32]. The infection does not promote protective immunity, and recurrence occurs in up to 50% of cases treated, mostly after a year of primary infection [33]. Risk factors associated with high risk for PCP include percentage of CD4 + T lymphocytes <14%, previous episodes of PCP, oral candidiasis, recurrent bacterial pneumonia, intentional weight loss and high plasma HIV load [34].

Pneumocystis jirovesi can colonize the respiratory tract of an individual without causing any signs or symptoms of infection; although the clinical significance of colonization is not yet well understood, patients who are colonized with the fungus can serve as a pathogen reservoir. They may also be at risk for developing pneumonia or transmiting the fungus to others. Individuals who are undergoing anti-Pneumocystis prophylaxis may develop colonization due to the selection of mutations that may be associated with anti-microbial resistance [35].

Pneumocystis has an incubation period of 3 to 12 weeks [36]. It features a unique tropism for the lung, where exists mainly as a cellular pathogen without invading the host [37]. Regardless of its source of transmission, infection is initiated by the invasion of fungic propagules on type I pneumocytes in alveoli [38], causing an intra-alveolar pneumonitis by occupying the airspace with exudate rich in protein and trophozoites. The result is an arteriovenous intrapulmonary shunt, thickening and disruption of the cellular membrane and parenchymal inflammation with subsequent mononuclear infiltrate, alveolar edema and fibrosis [39].

The inflammatory response in the lower respiratory tract is much diminished in AIDS patients when compared to the response in immunosuppressed individuals without AIDS, which is consistent with the fact that the fungal load in the lung tissue is much higher in individuals with AIDS when compared to the immunosuppressed without AIDS [40].

The PCP is characterized by severe neutrophilic lung inflammation which may result in diffuse alveolar damage, impaired gas exchange and respiratory failure. In fact, respiratory failure and death are more related to the degree of inflammation of the lung than the load of the microorganism in pneumonia [41].

Clinical Apresentation and Diagnosis

Pneumonia by pneumocystis jirovesi is, in most cases, the AIDS-defining illness in HIV-infected patients, and it occurs more often when the T helper cell count (CD4 +) is less than 200 cells / mm³ [42].

In HIV infected patients, PCP generally has a more subacute course and a bigger duration of symptoms than in other immunocompromised patients [43]. The clinical manifestations, most often have an insidious onset with symptoms that can last for weeks to months before requiring hospitalization. It starts with progressive dyspnea, fever, non-productive cough and chest discomfort that gets worse over the weeks [26,44]. Typical physical examination finds are tachypnea, tachycardia and no changes in lung auscultation. In up to a third of cases, breath sounds may appear, and 30% to 40% presents with auscultation crackles, a late finding that suggests greater severity [35,33]. Other manifestations associated with patients with HIV are extremity cyanosis, weight loss, night sweats, chills and retrosternal chest tightness [39,21].

Oral candidiasis is the most common co-infection, constituting an almost universal finding. Fever is present in the majority of cases and it may be the predominant symptom in some patients [26,21]. Facial seborrheic dermatitis is also common. Some infrequent symptoms may occur, such as fever of unknown origin with few respiratory symptoms or even its absence and extra-pulmonary infection by Pneumocystis jiroveci. Extra-pulmonary disease is rare, but can occur in any organ, especially the ear, eyes, thyroid, spleen, gastrointestinal tract, peritoneum, liver and pancreas, and has been associated with the use of pentamidine aerosol for prophylaxis [21,26].

In the early stages, often, all exams are unaltered, including chest X-rays, which are usually normal in 5% to 10% of cases. This does not exclude the diagnosis, which should still be considered especially when CD4 + T cell count is less than 200 cells / mm3 [45]. The most common radiological image for PCP is a standard bilateral interstitial infiltration pattern that becomes homogeneous and diffuse with the progression of the disease, however, it may vary

depending on the degree of immunosuppression, the presence of other concomitant infections or use of pentamidine prophylaxis regarding pneumocystis [46]. Less common findings include miliary pattern, heterogeneous infiltration, solitary or multiple nodules, consolidation of focal or diffuse airspace (usually occur in more advanced stages of the disease), and upper lobe infiltrates in patients receiving aerosolized pentamidine [39,46].

Even less often, the PCP may present with unilateral or asymmetric opacities. Thin walls cysts or pneumatoceles are seen in 10-20% of cases. Pneumothorax may occur; in fact, HIV-infected patients with pneumothorax should be suspected for PCP. Cavitation, intrathoracic lymphadenopathy and pleural effusion are rare; their presence can indicate an alternative diagnosis [47-49]. In the presence of an unaltered chest radiograph, computed tomography (CT) of high resolution can be useful [46]. The high-resolution CT has high sensitivity (100%) and specificity (89%) to PCP [48]. A negative result can allow the exclusion of PCP.

A CT scan can diagnose the disease previously undetected by conventional radiographs, suggest the coexistence of other nosological entities, show characteristic or suggestive signs of a specific disease and guide the biopsy site. The most characteristic CT finding in these patients is the presence of areas with ground-glass attenuation, ie homogenous increased attenuation without obscuring vascular images.A geographical pattern or mosaic, with normal secondary lobes adjacent to diseased ones, can also be seen. The finding of this pattern in a patient with AIDS is very suggestive of PCP. The presence of cysts is also a common finding. The distribution can be diffuse or predominate in the upper lobes. Furthermore atypical manifestations of the disease can be found, including isolated lobar disease, parenchymal opacities with focal nodules, nodules or excavated masses, miliary pattern, endobronchial lesions, pleural effusions and hilar and / or mediastinal lymphadenopathy. Pleural effusion is rare, being noticed, in general, on patients under chemoprophylaxis [50]. The presence of significant pleural effusion and / or intrathoracic lymphadenopathy suggest the association of other infectious diseases or non- infectious, like Kaposi's sarcoma, tuberculosis or lymphoma [39].

The most prominent histopathological finding is the presence of foamy intra-alveolar exudate. It refers to a proteinaceous fluid containing parasites, fibrin and cellular debris. It is this accumulation of fluid that is responsible for the frosted glass pattern formation in the tomography. Thickening of the interlobular areas within the frosted glass may also occur, leading to edema and interstitial infiltration by mononuclear cells. The frosted glass pattern in association with thickened interlobular septa originates the pattern of paving tile. With disease progression, airspace consolidation areas can be seen. The presence of cystic spaces is common. Cysts can be roughly divided into two types: Subpleural and intraparenchymal. Cystic lesions have a predilection for the upper lobes and subpleural regions, and there may be spontaneous pneumothorax [50].

The blood count reveals lymphopenia as the most common finding. Other hematological abnormalities such as leukopenia, anemia and thrombocytopenia can also occur [39]. The most common laboratory abnormality associated with PCP in HIV-infected patients, present in 90% of cases, is the high level of lactate dehydrogenase (LDH), it being significant for the prognosis [51]. However, a high level of LDH can occur with other pulmonary diseases, especially mycobacteria and fungal infections. Recently, low levels of S-adenosylmethionine plasma were shown as sensitive and specific indicators of PCP. Moreover, the levels increased with the successful treatment of PCP [52]. Probably the increase in LDH it is more a reflection of underlying lung inflammation and attack rate than a specific marker for the disease [39,46]. However, LDH levels above 500 IU / l, due to initial manifestations are associated with an increased risk of fatal evolution [47].

Regarding exercise oximetry, we can observe a decrease in arterial O2 saturation during controlled physical effort; however, this test is seldom used in our midst. Arterial blood gas analysis is mandatory and provides important information, being the finding of PaO 2 <60 mmHg very suggestive, showing severe hypoxemia that sometimes does not reflect the clinical status of patient [47]. Other findings include hypocapnia and respiratory alkalosis. Hypoxemia and hypocapnia may occur even before the appearance of lesions on chest radiography. It also serves to assess severity and monitor the progression of the disease [39]. The episodes are considered mild when the PaO2 (partial pressure of arterial oxygen) is above 70 mmHg or A-ADO2 (of alveolar-arterial oxygen difference) is below35, while in moderate to severe episodes PaO2 is below 70 mmHg or A-ADO2 is above 35 [21].

Because the microorganism cannot be cultured, PCP is diagnosed by direct microscopic examination of sputum, bronchoalveolar fluid or pulmonar tissue [46]. A sputum analysis induced by hypertonic saline inhalation is the least invasive and faster method available. However, as most of these patients do not produce sputum spontaneously, this noninvasive initial approach can be difficult. While the specificity of this method approaches 100%, the sensitivity ranges from 55% to 92% [31,53]. A bronchoscopy with bronchoalveolar lavage (BAL) is the gold standard for diagnosing PCP, with a reported sensitivity of 90-98% [31]. However, bronchoscopy requires specialized personnel, rooms and equipment, is expensive and carries a risk of associated complications. Thus, bronchoscopy is limitedly available in many areas of the world who are burdened with HIV / AIDS; therefore a non-invasive procedure for diagnosing PCP would be a significant clinical advance [54].

The use of polymerase chain reaction (PCR) has been shown to have good sensitivity and specificity for the diagnosis of PCP in induced sputum samples and washed broncoalveolar fluid [46]. Until the present time PCR has not replaced the clinical microbiology methods for the detection of fungus in bronchoalveolar lavage or induced sputum. The clinical significance remains under investigation, mainly due to the false-positives [34].

The open lung biopsy is rarely necessary [39]. Its indication should be limited to infrequent and well defined situations, such as: a) patient with diffuse lung disease that does not manage to induce sputum and with negative bronchoalveolar lavage and transbronchial biopsy; b) patient with a bleeding disorder, wherein the washing was negative; c) patients requiring mechanical

ventilation and in whom both, the washed and transbronchial biopsy, were negative. Even in these situations, it is advisable to hold a second bronchoscopy with biopsy and washing before proceeding to the open biopsy [46].

Cases of immunosuppressed patients with insidious fever lung disease demands further investigation of possible differential diagnoses, such as lung diseases caused by mycobacterial infections, pulmonary toxoplasmosis, fungal infections, CMV disease and cancer, that often have indistinguishable clinical presentation and radiological characteristics [39,55].

Patients with clinical manifestations of PCP associated to an increased risk of fatal outcome consists of elevated serum LDH> 500 IU / l, PaO2 <70 mm Hg or A-ADO2> 35, low concentrations of triiodothyronine (T3) and T3 reverse more than 5% of neutrophils in bronchoalveolar lavage, leukocytosis> 12,000 cells / mm3, albumin <2.8 g / dL. Previous episodes of PCP and / or recurrent pulmonary infections are also associated with worse prognosis[39,21].

Treatment

Treatment of PCP is guided by the patient's clinical severity [50]. Thus, for therapeutic purposes, we rank the PCP as mild, moderate and severe. Sulfamethoxazole with trimethoprim (SMX + TMP) is the recommended first-line treatment for HIV-infected patients with mild, moderate or severe PCP, being the intravenous therapy generally recommended for patients hospitalized with moderate to severe disease and the oral therapy recommended for non-hospitalized patients with mild cases [26].

In cases of mild to moderate pneumonia (PaO2 ≥ 70 mmHg), it is used SMX + TMP, with 15-20 mg trimethoprim / kg / day, orally, every six to eight hours for 21 days. The alternative regime in case of intolerance to sulfa is 300 mg of clindamycin, orally, every six hours plus 15-30 mg of primaquine, orally, once daily for 21 days. In the moderate to severe pneumonia (PaO2 <70 mm Hg) the choice route of administration is intravenous. The change of intravenous to oral administration must be performed when there is clinical improvement. The regime of choice is the association of sulfamethoxazole + trimethoprim (5 mg / kg of trimethoprim), intravenously, every six to eight hours. The full-treating time is 21 days. 600 mg of Clindamycin, intravenously, every six to eight hours plus 15-30 mg of primaquine, orally, once daily or pentamidine 4 mg / kg / day, intravenously, for 21 days are the main alternative schemes in case of intolerance to sulfa [56].

Adjuvant corticosteroids are associated with the treatment of PCP when PaO2 <70 mm Hg in air or alveolar-capillary gradient> 35 mmHg. The most common association is of Prednisone 40 mg orally twice daily for five days, halving every five days until the completion of the treatment at 21 days. Alternatively, one may use intravenous methylprednisolone equivalent to 75% of the dose prednisone. The initiation of treatment with corticosteroids should be performed at the same time as the PCP therapy [56,25]. The drug of choice for the treatment of PCP for children is also SMX + TMP. Adjuvant therapy with corticosteroids is also indicated in this population [57].

Prophylaxis

SMX + TMP are the drugs of choice for primary and secondary prophylaxis against PCP. Adolescents and adults infected with HIV, including pregnant women, should receive PCP prophylaxis if their CD4 + cell count is below 200 cells / mm3 or if they have a history of oral candidiasis (primary prevention) and after an episode of PCP (secondary prophylaxis) [50]. HIV-infected children with CD4 + lymphocyte count of less than 200 cells / mm3 or less than 15%, children 1-5 years on CD4 + less than 500 cells / mm³ or less than 15% and all HIV-infected children younger than 12 months regardless of CD4+ count should receive chemoprophylaxis [58]. Children born from infected mothers should receive prophylaxis between 4 and 6 months of age [57].

The preferential treatment is one tablet of 400-800 mg twice daily. Alternative regimens include dapsone with or without leucovorin and pyrimethamine, atovaquone suspension and aerosol pentamidine. Once started, the PCP prophylaxis is recommended for life, but it can be stopped in adolescents and adults with HIV infection who responded to HAART with an increase in CD4 + lymphocyte count to more than 200 cells / mm³ for at least 3 months [26].

Oral-Esophageal Candidiasis

Introduction

Oral- esophageal Candidiasis is a fungal infection, caused by Candida sp, with C. albicans being the species most commonly isolated. This fungus normally lives in mucosas and only causes disease when there are pre-existing conditions that favors its growth, the so called predisposing factors. It's estimated that 30 to 50% of people possess the microorganism in their mouths without evidence of clinical infection. The incidence increases with age, being near 60% in patients over 60 years of age that have teeth [59].

Oropharyngeal candidiasis (OPC) and oral- esophageal candidiasis (OEC) are by far the most common fungal infections in patients infected by the human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS). They are indicators of profound immunodeficiency and are more frequently observed in patients with TCD4 + lymphocyte count of < 200 cells, being OEC found in a more advanced stage of AIDS than OPC [60,61]. The prolonged course of infection by the HIV predisposes the patients to recurring episodes of candidiasis that can increase in frequency and severity during the HIV disease [62].

Epidemiology

Candida spp. colonizes the skin and the mucosal membranes of the genital and gastrointestinal tract as well as the oral cavity in a healthy individual under normal conditions [63]. The oral cavity is colonized in about 40-60% of healthy people. In HIV+ individuals, the asymptomatic colonization rate is higher, being approximately 76% [64]. The colonization by Candida and the invasive oral cavity infection occurs more often in HIV positive patients [65]. The genus Candida is currently classified in the *Saccharomycetes* class and *Saccharomycetaceae* family based in its gene sequence [66]. The genus Candida is comprised of a

dichotomous unicellular yeast specie measuring approximately 2 to 6 µm that reproduces by budding, being able to grow either as yeast or as a pseudohypha; most of the species forms pseudohyphas and hyphas in the tissues. The colonies vary in color from white to tan and they can have either a smooth or rough surface [67-69].

In fact, oropharyngeal candidiasis is the opportunistic infection most frequently found in individuals that have AIDS. The disease occurs in up to 90% of patients during the progression of the HIV infection. The occurrence of OPC, besides being associated with TCD4+ lymphocytes level under 200cells/mm3, is also correlated to a high viral load (>10.000 copies/ml) and to the HIV disease progression [70,71]. Although the C.albicans species seems to be prevalent in OPC, the epidemiology of this infection is rapidly evolving and non- albicans Candida species, as well as rare yeast forms, are appearing as the main opportunistic pathogen. The most common non-albicans Candida species are C. glabrata, C. parapsilosis, C. tropicalis and C. krusei., often isolated in oral and systemic candidiasis [72,73].

In a Brazilian study done with 80 HIV+ individuals , in which were collected saliva samples and candidiasis lesion samples (7 patients with OPC), the C. albicans was the species most often isolated in both, the saliva of patients without clinical lesions (49%) and patients with oropharyngeal candidiasis. Among the non-albicans, C. glabrata was the species most frequently isolated [74]. According to REDDING et al., the C. glabrata emerged as a notable pathogen in the oral mucosa, being it as a co-infecting agent with C. albicans or as the only detectable species in oral lesions. Furthermore, the C. glabrata associated with candida oropharyngeal infections in HIV positive patients tend to be more severe and difficult to treat than infections exclusively by C. albicans [75]. Other studies also show predominance of C. albicans in their samples [76,77].

Esophageal candidiasis is the main AIDS- defining disease, and its prevalence varies from 10% to 16%. In a control group study with patients infected by the HIV, the prevalence of cases was of 25,3% in the HIV infected patients and of 0.9% in the control group (patients not infected by the HIV submitted to an upper GI tract endoscopy) [78]. In this study, C. albicans was the one most frequently isolated (93,5%). In the esophagus C. albincans was the microorganism most often isolated, followed by C. dubliniensis, C. glabrata, C. krusei and C. tropicalis [79].

With access to antiretroviral therapy, the incidence of oropharyngeal and esophageal candidiasis has declined in HIV infected patients. However, such diseases continue to be a significant problem in places with limited resources or for those with a poor immune response, despite the realization of treatment [80,81].

Pathogeny

Candida lives as a commensal yeast in the human organism. However, under immunocompromising conditions the incidence as a carrier can increase and rapid conversions to symptomatic infections can occur [82]. The protections against the conversion from colonizing yeast to opportunistic/ invasive pathogen are provided by both, the systemic and local immunity. The Th-1 type immunity provided by T CD4 lymphocytes is a critical protection component, and the secondary defense is provided by TCD8 lymphocytes and oral epithelial cells by a variety of mechanisms [83].

The TCD4+ anti-candida protection mechanism, in a mucosa level, is not yet entirely comprehended. Recently, researchers have shown that cytokines, especially interferon gamma, can inhibit the transformation of candida blastoconidea to the more invasive hyphae phase [84]. Moreover, various researchers showed that the decrease in levels of E- cadherin and a loss of TCD4+ cells in the mucosa are associated with acute episodes of OPC [85]. The most commonly described cause of a high rate of yeast in the GI tract and of oral candidiasis is antibiotics use [84,86]. The eradication of bacterial competition is, almost certainly, the most important mechanism by which the antibiotics affect the candida quantity in vivo.

It is believed that various secondary lines of defense are important for the protection against candida when the primary defense done by the T CD4+ cells is insufficient. This secondary line of defense includes T CD8+ cells and oral epithelial cells. In individuals susceptible to OPC, the T CD8+ cells migration to outside the epithelial tissue is inhibited because of the reduction of E-cadherin with subsequent decrease in epithelial cells activity level against candida, resulting in the disease. E-cadherin in normal levels promotes the migration of TCD8+ to outside the epithelial tissue to fight against candida. It is believed that the increase in candida levels ensues in an increase degradation of E-cadherin, what creates a more suitable environment to the infection and development of OP [87,88].

A variety of virulence factors contribute to the pathogenicity of Candida spp. including the capacity to modify cellular morphology, ability to adhere to epithelial cells and the capacity to secrete extracellular enzymes, like phospholipases and aspartyl proteinases [89,90]. The phospholipases participate in the degradation of the phospholipids in the host's cellular membrane while the aspartyl proteinase degrades various physiologically important substrates like the albumin proteins and skin's immunoglobulins, contributing to the tissue penetration by Candida spp and subsequent host invasion during the process of infection [91,92].

In contrast to the oropharyngeal candidiasis, little is known about the host factors and operational yeast in the pathogeny of esophageal candidiasis and experimental models have not been established. However it is probable that the yeast's virulence factors and defects in the host's defense mechanisms are responsible. Esophageal candidiasis in HIV positive patients can be the first AIDS manifestation. The high prevalence of esophagitis in connection with AIDS indicates the critical role of cell mediated immunity to protect the esophagus against Candida invasion [93].

Regarding predisposing factors for oropharyngeal candidiasis in the HIV+ patient, the reduction of CD4+ lymphocytes to less than 200 cells/mm3 continues to be the most important factor for colonization by candida and the development of OPC [82]. However, other factors can influence the defense mechanisms that limit the Candida proliferation. The following can be found

among them: antifungal therapy, gender, use of dental prosthesis, tobacco use, intravenous drugs use, saliva flux rate, antimicrobial saliva constituents, lysozyme release and oral mucosa's immune system [94,95], alcohol use, feminine gender, and a high viral load [96].

Candida albicans oxidizes ethanol in the saliva, what leads to an unexpected high level production of acetaldehyde. This product affects the oral mucosa, increasing its permeability, causing atrophic areas in the epithelial surface that has become poor in extracellular lipids due to the alcohol use. Glucose concentrations of 18 g/dL, easily obtained from beverages, increases biofilm formation and C. albicans adhesion, what facilitates the occurrence of OPC [97]. The correlation between the feminine gender and OPC remains uncertain. It is believed that estrogen level deregulations can predispose an oral mucosa colonizing phase by C. albicans. This hormone would act as a protection factor for vaginal candidiasis and possibly, in lower estrogen levels, both the oral and vaginal tissue continues to be more susceptible to fungal infections [98].

In a study with 2.499 men with HIV and a baseline of T CD4+ cell count higher than 200 cells/ microliter, smoking increased the pseudomembranous candidiasis level risk by 40% (p less than or equal to 0.01) [99]. However, another study (139 people with HIV) suggested that tobacco use was not a risk factor for those individuals with a T CD4+ cells baseline count of less than 200 cells/ microliter [100]. The exact mechanism of action by which tobacco predisposes Candidiasis it is not known but it is believed that it compromises local immunity, inducing changes in cytokines and reducing anti-candida epithelial cell mediated activity [99]. Smoking has short and long term effects in many important aspects of inflammatory and immune responses in the oral cavity [101]. Cigarette smoke stops the neutrophils transmigration through the oral and periodontal microvasculature, suppresses the neutrophil cell diffusion, chemokinesis, chemotaxis and phagocytosis, and results in the release of neutrophil proteases, which can be an important mechanism in the destruction od tissue [102].

Regarding esophageal candidiasis, a low T CD4+cell count and a higher HIV-RNA viral load were identified as clinical factors associated with OEC, while the most severe endoscopy results were associated with lower T CD4+ cell counts [103]. Pharmacological suppression of the production of gastric acid, previous vagotomy, antibiotics use, functional or mechanical esophageal alterations and endocrine diseases like diabetes mellitus, hypothyroidism and hypoparathyroidism are among the risk factors for OEC. Malnutrition, alcohol use, advanced age and corticosteroids therapy have also been implied.

The IP, protease inhibitor, an important antiretroviral therapy component, has been associated, by a variety of authors, to the decrease in frequency of oral candidiasis by the drugs direct action against the yeasts [104,105]. In vitro studies have shown that the IP can inhibit aspartic proteases secreted by C. albicans and considerably attenuate their adhesion to epithelial cells, break the yeast cell membrane integrity and diminish candida's viability. These results support the idea that oral candida colony reduction in HIV infected patients that receive antiretroviral therapy might not be only due to the immune system's recovery, but also can result from a direct inhibition effect on the aspartic proteases by IP [106-108].

Clinical Presentation

There are different types of oropharyngeal candidiasis and they are classified in three groups: acute candidiasis, chronic candidiasis and angular cheilitis (stomatitis). Acute candidiasis is divided in pseudomembranous candidiasis, acute atrophic candidiasis (induced by dentures) and median rhomboid glossitis [109]. Among HIV+ individuals, the erythematous, pseudomembranous and angular cheilitis types are more evident. The erythematous and pseudomembranous types have a higher incidence, followed by angular cheilitis [110]. Pseudomembranous candidiasis is considered the most prevalent fungal infection in patients infect by HIV and has been associated with the progression of the disease; also it is utilized as a clinical marker to define the severity of the HIV infection [111].

Pseudomembranous candidiasis is clinically characterized as white- yellowish plaques, with a gelatin consistency that presents growth in the centrifuge and confluence [112]. The plaques are composed by entwined hypha mass, yeasts, desquamated epithelial cells and necrotic tissue fragments. These plaques can be removed by regular scratching with a rigid instrument or by friction with a dry gauze compress or a cotton swab, leaving as a result an erythematous, hyperemic, eroded or ulcerated surface with hemorrhage points, usually sensitive [112,60]. This allows the differential diagnosis between pseudomembranous candidiasis and hyperplastic candidiasis, being that in the hyperplastic candidiasis the plaques cannot be removed by scratching [113]. In most cases, these lesions are asymptomatic, with the exception of more severe cases where patients complain of sensibility, burning and dysphagia [69].

Acute erythematous candidiasis is a symptomatic lesion, generally associated with a burning sensation in the mouth or tongue. The tongue can be a brilliant red similar to the observed with low vitamin B12 serum levels, low folate and low ferritin [109]. There is intense sensibility due to the numerous erosions dispersed in the mucosa and due to the associated inflammation, most commonly located along the dorsum of the tongue, occurring also in the soft and hard palate. These lesions can cause a burning sensation when there is ingestion of hot or acidic aliments. It can occur independently or simultaneous to the pseudomembranous form [69]. The persistence of the pseudomembranous candidiasis can result in loss of the pseudomembrane with the development of a lesion known as acute erythematous candidiasis. Contrary to the pseudomembranous from, the oral symptoms of the acute erythematous candidiasis are much more accentuated due to the numerous erosions and the intense inflammation [112].

Angular cheilitis is a chronic inflammatory lesion characterized clinically by erythema, maceration, crusts and fissures. It affects the labial commissure and many times it is symptomatic and bilateral [114] causing discomfort. It can occur with or without erythematous or pseudomembranous candidiasis, and it can persist for a long time period if left without treatment [115]. The differentiation between each clinical subtype of candidiasis

is done by the appearance of the lesion and by the symptoms described by the patient. This way, the candidiasis should be differentiated from lichen planus, leucoplasia, Fordyce granules, eschar associated with chemical burns, traumatica ulcers, syphilitic plaques, keratotic lesions and discoid lupus erythematosus [112].

In regards to esophageal candidiasis, it mostly presents with odynophagia, dysphagia and retrosternal pain. Even though OEC can be an extension of the OPC, in approximately 10% of cases the esophagus is the only region involved, with OPC invading the distal two-thirds instead of the most often affected proximal one-third. One occasional characteristic of OEC is the complete lack of clinical symptoms even though there is an extended involvement of the esophagus [91]. In 20% to 50% of cases patients with OEC can be asymptomatic [116]. The differential diagnosis of OEC should include gastroesophageal reflux disease (GERD), idiopathic ulcers associated with HIV and viral esophagitis due to cytomegalovirus or herpes simplex virus [86].

Diagnosis

The diagnosis of OPC is generally clinical and followed immediately by empiric antifungal therapy. Initially, the clinical story should be collected, followed by a detailed mouth analysis including observation of the soft and hard palate and examination of the oral mucosa, after removing any prosthetics that the patient might have. Predisposing factors must be identified, as mentioned above, and resolved if possible and an evaluation of the type, severity and chronicity of the infection must be done [109]. In case of recurring candidiasis, candidiasis resistant to previous treatment and/or patients repeatedly exposed to fluconazol (and/or imidazole derivatives), the identification of yeasts through fungal direct exam, cultures and susceptibility tests to antifungal agents are recommended due to the possibility of infection by Candida spp resistant to one or a varitety of triazole drugs [117-119].

In cases of esophageal candidiasis in HIV+ patients, the presumptive diagnosis can be generally done after the beginning of typical symptoms or by the presence of oral candidiasis associated with esophageal symptoms and the antifungal treatment can be empirically initiated. An endoscopy before the beginning of antifungal therapy can be done in those individuals without concurrent OPC or those with atypical symptoms. If the patients does not improve with adequate systemic antifungal therapy an endoscopy is recommended so that other causes of esophagitis mentioned earlier can be excluded [82]. The endoscopy can reveal white plaques that may or may not be accompanied by ulcerated lesions. It is also recommended that a sample be obtained for microscopic exam, culture and a mucosa biopsy [117].

Treatment

When choosing an antifungal agent for the appropriate treatment of OPC and OEC a number of factors should be considered, including previous exposure to antifungal agents and correct species identification [120]. The treatment's objectives are to eliminate the signs and symptoms of the disease, reduce or eliminate colonization and avoid recurrences [121]. Fluconazole continues to be the antifungal drug of choice for OPC and OEC treatment. Fluconazole is a fungistatic against Candida spp. with an oral bioavailability superior to 80%, which is not influenced by concomitant food ingestion or gastric pH. Its penetration in the saliva is excellent. Because of its hepatic metabolization through the CYP450 enzyme, many drug interactions with fluconazole were described [120]. However, the appearance of Candida species resistant to fluconazole in vivo and in vitro has been well documented [122,123]. C. glabrata and C. krusei are frequently resistant to fluconazole [124].

Fluconazole, in the dosage of 100mg/day during 7 to 14 days is recommended as the first choice drug for OPC treatment [125]. Alternatives to fluconazole include mucoadhesive miconazole tablets, 10 or 50mg/ day during 7 to 14 days. Itraconazole solutions during 7 to 14 days (100 or 200mg/day) is equivalent to fluconazole during 14 days. Itraconazole has a higher oral bioavailability and a higher incident of drug interactions when compared to fluconazole. Posaconazole (200mg in the first day and 100mg/ day for the remaining days) is also an alternative to fluconazole; it is considered a therapy option in cases with fluconazole resistant Candida sp. Topical agentes should not be used for treatment of OPC due to its low tolerability (sour flavor, gastrointestinal effects, frequent dosage) and less efficiency [125-127].

Oral administration of fluconazole (200mg/ day during 14 to 21 days) is the therapy of choice for OEC. Intravenous formulations can be used in severe esophagitis cases. Topical agents are not sufficiently efficient and should be avoided [126,128]. Itraconazole (oral solution) is and alternative agent, that has been described to be as clinically and mycologically efficient as fluconazole [82]. Voriconazole, 200mg two times per day for 14 to 21 days, is as efficient as fluconazole, but it is associated with a higher incidence of adverse effects and a higher potential for drug interactions, visual alterations and phototoxicity in ambulatory patients [128]. Echinocandins were evaluated for the treatment of OEC associated with AIDS, especially comparing it to fluconazole. Intravenous caspofungin, micafungin and anidulafangin can be used, however, these agentes have a higher recurrence rate then fluconazole, are more expansive and are not available in an oral formulation [82].

Refractory OPC or OEC is defined as symptoms that persist for more than 14 days of treatment with 200mg/day or more of fluconazole. This syndrome is described in approximately 5% of HIV infected patients, generally in those with a T CD4+ cell count lower than 50cells/IL that received antifungal/ triazole agents multiple times or for a prolonged time due to a high number of OPC episodes [129]. Any use of topical antifungal agent, like amphotericin B, should be avoided because of its low efficiency rates. The use of Fluconazole in a more elevated daily dose can be beneficial, at least temporarily, particularly the oral suspension, due to its increased saliva concentrations. Itroconazole solution (up to 600mg/day) it is an alternative and it's associated with a response rate of 55-75%, however recurrences occur posteriorly. Posaconazole oral suspension (400mg, twice a day for 29 to 90 days) can also be utilized and it's efficient in up to 86% of patients with oropharyngeal candidiasis and/or fluconazole/itroconazole-refractory esophageal candidiasis. Caspofungin can be used in

HIV infect patients with fluconazole-refractory OEC. Amphotericin B, amphotericin B lipid complex, and liposomal amphotericin B can also be efficient in the previous scenario, but considerable attention should be given to their toxicity profiles [120,130-132].

Prophylaxis

Despite the proved fluconazole efficiency, antifungal primary and/ or secondary prophylaxis for the prevention of OPC and OEC is not recommended. The disadvantages of primary prophylaxis include the potential for drug-interactions between the triazoles and the highly active antiretroviral therapy (HAART), the development of fluconazole resistance and/or cross resistance to azoles, the toxicity and the cost of antifungal therapy. Therefore, the best prophylaxis for both OPC and OEC is the adequate use of HAART [126,133].

Neurotoxoplasmosis

Introduction

The neurotoxoplasmosis, or cerebral toxoplasmosis, is the infection of the brain by the protozoan Toxoplasma gondii [134]. The T. gondii was first described in 1908 in Tunisia, by Nicolle and Manceaux [135] and was reported in Sao Paulo, Brazil in the same year [136]. Only 15 years later, in 1923, the parasite was found in humans and only in 1942, in cats. In 1967 it was discovered that the T. gondii could be contracted through the feces of Felidae, which were defined as the definitive hosts in 1970 [135].

Epidemiology

About a third of the world population is chronically infected with the parasite T. gondii, and the majority of cases are asymptomatic. However, toxoplasmosis can cause serious consequences in immunocompromised individuals or in cases of congenital infection [137]. The prevalence of seropositivity for T. gondii varies according to the individual's home region, it is estimated that the prevalence in the US is between 15% and 29.2%, while in tropical countries in Europe this rate can reach up to 90% [138].

As for neurotoxoplasmosis, despite the drop in the number of cases due to the implementation of antiretroviral therapy (highly active antiretroviral therapy or HAART), it continues to be the main opportunistic infection in the central nervous system in people with AIDS and the one who causes more focal lesions in brain [139-141].

Before the HAART implementation, prior to the mid-90s, the annual incidence of neurotoxoplasmosis in HIV-positive individuals with advanced immunosuppression was about 4 cases per 100 people. With the implementation of therapy the annual incidence of neurotoxoplasmosis reduced 75%, ranking only 1 case per 100 patients [142]. However, in some countries where the seroprevalence of toxoplasmosis is high, the incidence of toxoplasmosis is estimated at up to 40% among patients with AIDS who not receive the correct prophylaxis[140].

Pathogenesis

The lifecycle of T. gondii is characterized by being heteroxen, requiring two or more hosts for its occurrence. Members of Felidea family are the definitive hosts, or complete, as they present the enteroepitelial cycle, or sexual, and the extraintestinal or asexual cycle. All the other warm-blooded animals showing only the asexual cycle are referred to as intermediate or incomplete hosts [143].

In felines, as a result of the sexual phase, occurs the formation of oocysts[146] which are released in a non sporulating way to the outside environment via the faeces. After a period of 1 to 5 days oocysts become sporulated and virulent [145]. The felines eliminate oocysts in feces for only a short period in its life. After 2 weeks from initial contact with the parasite the felids initiate the development of immunity [146], decreasing the rate of multiplication and disposal of the T. gondii [147]. However, despite the short period of elimination of oocysts, a large amount of them are released to the external environment and, in addition, the oocysts are very resistant to chemical and physical agents in the environment, which makes them viable for months or years [148].

After the oocysts are released in the external environment, the intermediate hosts can become infected by ingesting soil, water or contaminated plant material [145]. Upon being ingested, oocysts become tachyzoites, which multiply rapidly characterizing acute or active infection [149]. These organisms have a predilection for neural and muscle tissues, which is where the tachyzoites will result in bradyzoites that multiply slowly and form cysts, featuring chronic infection [150].

With this, in addition to infection by direct ingestion of oocysts, the felines and humans can become infected by ingesting the cysts of T. gondii bradyzoites from other animals, which occurs by ingestion of raw or undercooked meat. Adding to these ways of infection, humans can acquire the parasite through blood transfusion, by organ transplantation or via the placenta [145].

It is suggested that neurotoxoplasmosis in immunocompromised individuals, usually (95% of cases) results from reactivation of latent bradyzoites cysts[151].

Cysts reactivation occurs when the person is already in a severe stage of immunosuppression. The neurotoxoplasmosis may appear in individuals who have a T-lymphocytes CD4+ count lower than 200 per microliter. The risk of reactivation of cysts increases with lower CD4+ levels. The increased risk of developing the disease occurs when the CD4 + T-cell count drops to levels below 50 cells per microliter [152].

With the immunosuppression, occurs a breakdown of tissue cysts formed by protozoa and the release of bradyzoites, which multiply in place and later migrate to other organs. The injury by infection of Toxoplasma gondii is caused by cell invasion that starts a lysis process and consequently leads to cell and tissue destruction [153].

The reactivation of the cyst causes a conversion of bradyzoites in tachyzoites [154]. In a person with normal immunity and with tachyzoites present in the blood T-lymphocytes CD4+ are activated and enable the release of the CD154 molecule (also called CD40 ligand), that stimulates dendritic cells and macrophages to secrete Interleukin 12 (IL-12), which prompts T-cells to produce

interferon gamma (IFN-γ), stimulatating macrophages and other non phagocytic cells to carry out a anti-toxoplasmic response. The tumor necrosis factor (TNF-a) also have proved to be important in controlling infection by developing an intense response from T cells. With this adequate immune response, tachyzoites would become bradyzoites. In HIV-positive patients, however, the expression of CD154 in response to T. gondii is impaired, so the entire cascade response against the parasite will fail [155].

A study conducted in São Paulo, Brazil, compared IFN-γ, TNF-a and interleukin-10 (IL-10) levels in four patient groups: (1) those with AIDS and neurotoxoplasmosis, (2) patients with ocular toxoplasmosis, and other two control groups; (3) chronically infected patients and (4) healthy patients. The result was that patients with AIDS and neurotoxoplasmosis and those with ocular toxoplasmosis have higher TNF-a levels than control subjects and lower IL-10 and IFN-γ levels. The IFN-γ is required for the prevention of the reactivation of dormant cysts during chronic infection. TNF-a is directly involved in regulating growth of tachyzoites, however, as explained above, it depends on the action of T cells. Thus, IFN-γ and TNF-a levels reflect the efficiency of the protective functions against infection by T. gondii. However, knowledge about the pathophysiology of cerebral toxoplasmosis remains incomplete [156].

Clinical Presentation

The symptoms of neurotoxoplasmosis consist of headache, confusion or altered mental status, fever, lethargy, convulsions, changes in coordination, focal muscle weakness, nausea or vomiting, visual disturbances, incontinence and neck stiffness. Signs of neurotoxoplasmosis consist of focal signs (hemiparesis, ataxia, paralysis of cranial nerves, sensory deficits, aphasia, hemianopia), axillary temperature greater than 38.4 degrees Celsius, abnormal level of consciousness, psychomotor retardation, meningism and behavioral disorders. However, the main clinical findings of toxoplasmosis are headache, confusion or altered mental status, fever or convulsions[157].

Untreated neurotoxoplasmosis cases can progress to coma within days or weeks. Rarely, toxoplasmosis may present as a rapidly progressive and fatal form of diffuse or global encephalitis with severe mental status changes, nausea or vomiting that often indicate elevation of intracranial pressure [158].

Diagnosis

According to the Centers for Disease Control (CDC), the diagnosis of neurotoxoplasmosis in AIDS patients should be assumed according to the sum of three situations: (1) recent onset of focal neurologic abnormality that is consistent with intracranial disease or level of reduced consciousness, (2) evidence in diagnostic brain imaging (CT or MRI) of a lesion with mass aspect and (3) antibodies to T. gondii present in plasma or satisfactory response to treatment for toxoplasmosis [159]. The therapeutic success can be translated by improvement in the clinical and radiological findings with reduced neurological signs and symptoms after the implementation of drug treatment [160].

Infection with T. gondii is initially detected by the demonstration of specific antibodies against the parasite. A range of different serological tests, known as Toxoplasma Serologic profile (TSP), evaluate different antibodies to T. gondii and serum levels of these antibodies can increase or decrease according to the evolution of infection [161].

The presence of anti-Toxoplasm IgG becomes positive in the first 2 weeks after infection, has its peak between 1 and 2 months after primary infection and remains positive throughout the patient's life, therefore, it is not considered an accurate marker of infection, even if it indicates the improbability of infection when the IgG is negative. Furthermore, the presence of IgG can not distinguish latent from active infection [161,162]. The anti-Toxoplasm IgM antibody appears before and decays faster than the IgG antibody. In patients infected with recently acquired T. gondii, the presence of IgM is detected initially and usually it decreases within a few months. Serological tests for the detection of IgM are not specific and result in many false positives. Aside from IgM, IgA and IgE antibodies can be applied in the detection of acute infection and congenital T. gondii.

In immunocompromised patients chronically infected with T. gondii (IgG positive), the results may indicate an apparent reactivation of the disease with an increase in levels of IgG and presence of IgM [161]. However, IgM antibodies are usually absent in patients with reactivation of the disease and in HIV-positive patients with neurotoxoplasmosis [142]. Therefore when there is suspicion of toxoplasmosis in an HIV-positive patient chronically infected with T. gondii, additional serological tests will not add relevant information for diagnostic developments and other diagnostic methods should be bandied [161].

Imaging tests such as magnetic resonance and computed tomography, are indicated when the neurotoxoplasmosis is suspected in HIV-positive patients. These studies generally show multiple lesions located in the cerebral cortex, the cortico-medullary junction or in the basal ganglia [163].

Typical findings on computed tomography (CT) without contrast are: multiple hypodense lesions commonly with edema and mass effect on its periphery; completely resolved injuries or residual calcifications, posterior to treatment [164]. These lesions can be confused with other types of focal brain lesions and a new TC, this time with contrast, can demonstrate the typical sign "ring-enhancing".

Typical MRI findings are: T1 has a hypodense image, while in the T2 lesions present hyperdense (hypo-isodense standards or mixas can still be found) and the diffusion-weighted imaging (DWI) are Hyperintense. Yet, T1 image with gadolinium contrast shows the characteristic lesions in "ring-enhancing" (or rings realse), commonly circular and with hypointense signals (edema) [164]. The differentiation of neurotoxoplasmosis from a central nervous system (CNS) lymphoma can be difficult, as in lymphoma there is also the presence of edema and mass appearance in the periphery of the lesion, so to differentiate them it is indicated the acquisition of a positron emission tomography (SPECT) [165].

The evaluation of cerebrospinal fluid (CSF) is rarely used for the diagnosis of neurotoxoplasmosis due to risk of leading to intracranial hypertension; however, this procedure can be performed if there is doubt about the diagnosis [166]. The CSF

evaluation findings may include: high protein, varying levels of glucose and mild elevations in white blood cell count in the blood with a predominance of mononuclear cells [167]. Furthermore, neurotoxoplasmosis can be diagnosed by microscopic evaluation by the CSF technique "or Wright Giemsa stain", which can yield positive results in a variety of protozoa and helminthes [168]. The detection of T. gondii's DNA in body fluids, especially CSF obtained by lumbar puncture, by polymerase chain reaction (PCR) may also be performed to aid in the diagnosis of neurotoxoplasmosis, however, it is not usually performed [169].

Finally, pathological evaluation of brain tissue biopsy elucidates the definitive diagnosis of neurotoxoplasmosis and the findings of this method consist of tachyzoites or cysts surrounded by areas of inflammation. The T. gondii cysts may appear as solid or granular cysts, the latter being secondary to mesenchymal reaction of the glial cells that results in necrotizing encephalitis and focal vasculitis. The reactivation of T. gondii cysts can lead to brain abscesses with avascular central areas and the cerebral area surrounding the injury will demonstrate edema and inflammatory infiltrates with lymphocytes and plasma accumulation of other cells around the site vessel [170].

However, despite confirming the diagnosis of neurotoxoplasmosis, biopsy of brain tissue is not used routinely because of the risks involved in the process of obtaining the tissue and because the other diagnostic methods can promote a presumptive diagnosis with good confidence rate [170]. A biopsy is reserved for cases where there is diagnostic uncertainty or when the patient does not respond or worsens with empirical treatment [171,172].

Treatment

The treatment of choice for neurotoxoplasmosis is a combination of pyrimethamine with sulfadiazine (SDZ-Pyr). It is recommended the addition of leucovorinto to this therapy, to reduce hematologic complications due to the mechanism of the other two drugs that impair folic acid synthesis. However, most patients demonstrate intolerance to this combination therapy. In such cases and after failure of the first-line treatment (Pyr-SDZ) the therapy of choice is often the combination of pyrimethamine with clindamycin, also with recommendation to add leucovorin [142].

Classic regimen of SDZ-Pyr with leucovorin varies according to the patient's weight. If less than 60 kilos, a single initial dose of 200 mg of pyrimethamine will be administered orally (PO), followed by 50mg of pyrimethamine PO daily, sulfadiazine 1000mg orally every 6 hours and 10 to 25mg of leucovorin PO (can increase the dose to 50mg). For patients with more than 60 kilos, the maintenance dose of pyrimethamine is 75mg per day, of sulfadiazine is 1500mg every 6 hours and the dose of leucovorin remains the same [169]. In patients unable to take oral medication, the administration of 10mg/kg of trimethoprim plus 50 mg/kg intravenous sulfamethoxazole should be considered [170].

The acute treatment described above should be maintained for 6 weeks if the patient showed clinical and radiological improvement, however, if the lesions are extensive, or the response at 6 weeks is not enough, the time of administration of the therapy must be protracted. About 90% show clinical and radiological improvement from the second week of treatment with Pyr-SDZ.

In general, a rapid clinical improvement must be observed after treatment. On the third day, about 51% of patients showed neurological improvement (up to 91% at the end of two weeks) and beginning on the third week radiological improvement occurs. Those who do not get adequate response at the end of the first two weeks or worsen clinically by the third day must perform biopsy to rule out lymphoma [177]. Antibody titers are not trusted in the therapeutic response, so the patient should be evaluated clinically and radiologically frequently [142].

Anticonvulsants may be given to those who present seizures [142,171]. Antihistamines can be used for patients who show pruritus as an adverse reaction to sulfadiazine. Treatment in pregnant women is identical to that of other patients; however, the pregnant woman should be warned that sulfadiazine can cause hyperbilirubinemia and kernicterus in the baby [142].

Oral corticosteroid, such as dexamethasone (4 mg every 6 hours), can be considered as adjuvant therapy to patients in two cases: cases where the clinical condition worsened during the first 48 hours of treatment; or for those who have radiographic evidence of deviation of the middle cerebral line or signs of increased intracranial pressure [142]. Treatment with corticosteroids should be as short as possible because of the possibility of immunosuppression and patients should be monitored constantly to check for the emergence of other opportunistic infections [142,170].

Regarding antiretroviral therapy, it is not clear when medication should be initiated or re-initiated in an HIV positive patient with acute T. gondii infection and, in general, the medication can be administered again after the treatment of acute toxoplasmosis [178].

Prophylaxis

All HIV-positive patients, as soon as they are diagnosed with HIV infection, should have their IgG antibody for Toxoplasma evaluated, so it can serve as screening for the risk of toxoplasmosis development. To minimize the risk of being infected by T. gondii, HIV-positive patients should: avoid eating raw or undercooked meat, wash hands after handling raw meat and after contact with soil and wash fruits and vegetables before eating them. As for the domestic cat, the HIV-positive patients should require someone else who is not infected with HIV or who are not pregnant, to wash the cat's litter box. If this is not possible, patients should wash their hands after cleaning the box. Cats should not be fed raw meat, giving preference to manufactured cat food. Finally, patients with HIV should not be encouraged to give away their cats or to test their animal for toxoplasmosis [142].

The primary pharmacological prophylaxis is recommended for patients who are seropositive for Toxoplasma gondii and have CD4 counts of less than 100 cells per microlitre. Patients with CD4 counts of less than 200 cells per microliter and with an opportunistic infection or adjacent malignancy should receive primary prophylaxis as well. The drugs of choice are trimethoprim and sulfamethoxazole and must be administered daily. Primary

prophylaxis can be stopped as soon as the CD4 levels rise above 200 cells per microliter for three months [142,169]. Primary prophylaxis against T. gondii with trimethoprim and sulfamethoxazole in patients with CD4 counts less than 100 cells per microlitre reduced risk for toxoplasmosis in 73% [170].

Secondary pharmacological prophylaxis should be done for patients who have completed therapy for acute toxoplasmosis for 6 weeks successfully, the use of medication should be chronic, unless immune reconstitution occurs due to antiretroviral therapy. If the patient returns to levels lower than 200 CD4 cells per microliter, secondary prophylaxis should be reconstituted. Some studies propose the discontinuation of secondary prophylaxis based on the maintenance of good immune levels and the absence of clinical signs and symptoms, but none of them promotes a good level of clinical evidence.

Secondary prophylaxis is made with the combination of sulfadiazine, pyrimethamine and leucovorin. In this case, the doses of medications may be smaller than in the acute treatment of neurotoxoplasmosis. For sulfadiazine it is recommended the administration of 500 to 1000 mg orally 4 times a day (total of 2000 to 4000mg), for pyrimethamine it is recommended 25 to 50 mg per day and the leucovorin dose is 10 to 25 mg per day [142,171]. For patients that do not tolerate prophylaxis with sulfadiazine, it can be done with clindamycin instead. Atovaquone as monotherapy may be considered for patients intolerant to pyrimethamine [172], however, the failure rate is 26% in the first year[180].

Conclusion

Opportunistic infections, even in the era of antiretroviral therapy, remain a major problem in HIV-infected individuals. The occurrence of pneumocystosis, and thrush neurotoxoplasmosis represent, in most cases, markers of AIDS progression, representing an important public health problem nowadays.

Early detection of this disease, as well as knowledge on the epidemiology, clinical manifestations, diagnosis and appropriate therapy, allows for proper management in HIV + individuals, decreasing the chances of possible complications and evolution of the immunosuppression, improving the quality of life and reducing morbidity and mortality of these patients.

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