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Chapter

HIV-Associated Histoplasmosis

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Abstract

Impaired immunity induced by HIV is one of the main causes of disseminated histoplasmosis in endemic areas, and thus from 1987 WHO and then the CDC classified this condition as an AIDS-defining illness. Host factors associated independently with histoplasmosis are low level of CD4 (<150 cell/mm^3) and CD8 count, low nadir CD4, male gender, the absence of cART, the absence of systemic antifungals, and history of herpes simplex infection. Dissemination of an exogenously new acquired infection or reinfection and reactivation of a latent infection are both described in HIV-infected patients. Also, inflammatory reconstitution disease following cART initiation is possible. Acute pulmonary infection is rare, and only in HIV-infected patients with CD4 > 200 cell/mm^3. In advanced disease, the most frequent manifestation is as disseminated histoplasmosis often acute and severe, with complications such as respiratory failure, circulatory shock, and disseminated intravascular coagulation. The subacute presentation is frequent, associated with moderate involvement of the reticuloendothelial system, with great variability of clinical manifestation. Guidelines for diagnosing and managing histoplasmosis among people living with HIV have been published from WHO, IDSA, NIH, but limited data was based on randomized clinical trials.

Keywords: histoplasma capsulatum, immunocompromised patients, HIV, progressive disseminated histoplasmosis

1. Introduction

Histoplasmosis as an endemic mycosis, overlapping the HIV pandemic, creates the most interesting and common pattern of infection in immunocompromised patients: the progressive disseminated form (PDF). Histoplasmosis is not a contagious disease, but in hyperendemic areas [1] (as regions of North America [2], Central America, and South America [3]), and also countries from Africa [4] and Asia [5] it has been reported to be the second or the third most common opportunistic infection in HIV-infected patients [6–9]; thus, this co-infection continues to generate clinical, diagnostic, and public health challenges. From 1987 histoplasmosis was classified by WHO as AIDS-defining disease, and from 2020 the same entity released guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV [1].

2. Epidemiology

Histoplasmosis has been reported worldwide in tropical and subtropical, but most frequently, in temperate areas where this dimorphic fungus has found the perfect condition to thrive as mold (saprophytic form): nitrogen-rich soil at temperatures of 37°C or greater with moisture (95–100% humidity), containing bird droppings (composed of nutrients that promote growth and also substances that discourage the growth of competitive organisms), or bat guano.

However, what has significantly changed the global epidemiology of histoplasmosis was precisely the HIV pandemic, especially because of patients in the AIDS stage. In fact, HIV-infected patients often serve as sentinel markers for histoplasmosis outbreaks [6, 7].

Starting with 1983, several case reports have been published about HIV-infected patients who have been diagnosed with progressive disseminated histoplasmosis (PDH) [7]. Some of them came from endemic areas but a lot of cases have been discovered in places considered as non-endemic areas, which was not expected. In United States, reports have come from hyper-endemic areas such as Indiana [8, 9] as well as from areas where histoplasmosis has never been reported [10, 11] such as Denver or California.

Outside the United States, histoplasmosis incidence is driven by the AIDS pandemic [12]. In French Guyana, PDH is considered to be the most common AIDS-defining illness [12, 13], detected in 41% of HIV hospitalized patients with fever and CD4 less than 200 cell/mm^3. In the hyper-endemic area of Rio Grande do Sul, Brazil, 47% of patients diagnosed with histoplasmosis are HIV positive and have PDH [12, 14]. Between 1992 and 2008 in Columbia, 70.7% of the patient diagnosed with histoplasmosis had AIDS [12, 15, 16]. Two different studies estimated the incidence of histoplasmosis in Latin America to 1.48 cases per 100 PLWA, which amounts to over 22,000 cases per year [17, 18] (the first) and 0.15 per 100,000 person-years [18, 19] (the second), both estimation for 2012 and 2011. In the first study, countries with the highest histoplasmosis incidence in people living with HIV (≥1.5 cases per 100 people living with HIV) follow the same geographical distribution as histoplasmosis prevalence hotspots in the general population: Central America, Argentina, and the northernmost part of South America (Venezuela and the Guiana Shield) [17].

In parts of Asia [20], Southeast Asia [21], and India [22] where histoplasmosis is endemic, the most described and reported cases are in people living with HIV/AIDS. In China, 75% of cases are reported along the Yangtze River, most of them in association with AIDS [23].

In Africa, where HIV continues to be a major global public health issue [24], the estimated rate of histoplasmosis is not established due to the lack of solid epidemiologic studies and the limited possibility of detection in the laboratory. Cases of HIV patients have been reported in South Africa (Transvaal and Cape Province) [25], Zimbabwe [25], Uganda [26], Nigeria [27], and Tanzania [28]. Both strains of Histoplasma capsulatum are isolated in Africa. African histoplasmosis caused by H. capsulatum var. duboisii is prevalent in Western and Central Africa (Mali, Chad, Niger, Nigeria, Democratic Republic of Congo, and Ghana), and in the island of Madagascar [25]. Meanwhile, in South Africa and Zimbabwe, only the classical histoplasmosis caused by Histoplasma capsulatum var. capsulatum is known to occur [25] as is the case in the United States, Latin America, Asia, and Australia. Cases confirmed in HIV travelers who are returning home from these areas are diagnosed in Italy, Spain, the UK, the Netherlands, etc., as imported infections [29].

In Australia, where H. capsulatum has been found in Queensland and New South Wales from different samples (caves and fowl yards), only 63 cases have been

diagnosed, but 41% of disseminated disease occurred in patients with human immunodeficiency virus [30].

In Europe, a non-endemic area, only a few cases of histoplasmosis in HIV-infected patients have been reported. Most of them are imported (mainly from Central and South America), but there were also rare autochthonous cases (Italy and Israel). The time span between leaving the endemic area and the diagnostic could reach up to four decades. Due to the scarce knowledge of this disease, the prognosis is poor with a high mortality rate (32%) [29] as the delay of diagnostic is detrimental in the course of disseminated histoplasmosis.

Due to the PDH form recognized by clinicians, reports about this disease came from across the world in places where histoplasmosis had been rarely or never present: Thailand, where this disease is observed almost exclusively among HIV-infected patients as this country is facing a high HIV prevalence (1253 cases reported from 1984 to 2010) [31, 32], Trinidad (only two cases also in HIV men) [33], and the Democratic Republic of Congo [18]. These reports of HIV patients are proving to be very useful in order to identify previously unrecognized areas where histoplasmosis could generate different forms of disease. Conversely, detecting a case of histoplasmosis in an area considered non-endemic must require the patient's testing for a possible HIV infection.

If prior to the advent of HAART approximately 5% of AIDS patients living in endemic area developed histoplasmosis [34] with a peak of incidence during the Indianapolis outbreak of 27% [6], nowadays initiating cART rapidly proves to be the game changer for this comorbidity in HIV patients [35, 36]. As the "test and treat" intervention strategy provides good results with 79% of people living with HIV aware of their status and 62% receiving treatment in 2018, and as guidelines recommend that all HIV-patient must start cART regardless of CD4 count [37–39], and it is expected that the global epidemiology of histoplasmosis in HIV patients will be changing in the future, except in countries where ART access is still not widely available or the patients are non-adherent.

Occupational risk factors identified to be associated with histoplasmosis in AIDS-patients were working with birds [35] or history of exposure to chicken coops [40]. Among case patients who had worked with soil contaminated with chicken or bat droppings and who could recall the date of their most recent exposure, the median time from their last exposure to the onset of symptoms was of 1.6 years [35]. A notable risk factor was smoking; although not historically associated with progressive disseminated histoplasmosis, smoking has been recognized as a risk factor for the chronic pulmonary form of the disease [41]. Recipients of antifungal agents as any triazole in the 2 months prior to the diagnosis of histoplasmosis seem to have a lower risk, as well as history of Pneumocystis jiroveci pneumonia (PCP) [35, 42].

Several risk factors are associated with the progressive disseminated form: low CD4 lymphocytes count (less than 150) and low nadir CD4 count [40, 42], low CD8 count [42], history of chronic medical condition and history of herpes simplex infection [35], and male gender [42]. Receiving treatment with TMP-SMZ was associated with a decreased risk of poor outcomes [35]. Other described factors associated with severe manifestations of histoplasmosis are: a level of creatinine higher than 2.1 mg/dL and hypoalbuminemia (less than 3/5 g/dL) [43].

3. Pathogenesis

Similar to other systemic fungal infections, the primary infection occurs in the lung after inhalation of the aerosolized microconidia. When the conidia reach

the alveoli, the innate immune response is activated and the fungus binds to the CD11-CD18 family of integrins and is engulfed by neutrophils and macrophages [44, 45]. Once inhaled, the conidia transforms within hours into the parasitic yeast phase [18, 46]. Even though neutrophils emigrate early into infected foci of the lungs, these defense cells are fungistatic, not fungicidal, against Histoplasma capsulatum [47]. Macrophages and dendritic cells are the principal effector cells in host resistance to this fungus [44, 46], with a dual role in host defense for macrophages. H. capsulatum is able to replicate in macrophages until T cells will be activated, so the first role is to contain the yeast. The second role comes after cellular activation when several endogenous cytokines are released (IL-12, IFN-γ, TNF-α, and GM-CSF) and macrophages inhibit intracellular growth and harbor H. capsulatum, with granulomas formation [48, 49]. It is a protective mechanism to annihilate this fungus but also a repository for H. capsulatum that could lead to reactivation [48, 49]. Like tuberculosis, there is an early transport to regional lymph nodes with formation of a primary complex.

The link between innate and adaptive immunity is represented by dendritic cells that reside in the lung, as they are more potent than alveolar macrophages as antigen-presenting cells [50]. Dendritic cells have fungicidal activity and after phagocytosis will present H. capsulatum antigen to T cells, once they leave the tissues and travel to the lymph nodes. That generates the phase of adaptive immunity with lymphocyte proliferation and induction of cell-mediated immunity [51, 52]. T cells are crucial in clearance of H. capsulatum and this major implication is demonstrated by several experimental studies [53, 54]. Both CD4+ cells and CD8+ cells are necessary to induce a robust immune response [52, 55]. The adaptive immune response can either clear the organism of fungus or lead to granuloma formation. If the latter occurs, there is the potential for reactivation of the yeast. Reactivation is a response to impaired immunity. The primary contribution of T cells to host defense is the release of cytokines (IFN-γ, TNF-α, and GM-CSF) that will activate mononuclear phagocytes in order to control the infection.

HIV-infected patients are the perfect hosts for histoplasmosis especially in the late stage of AIDS. Depletion of CD4+ T cells and qualitative CD4+ T-cell dysfunction independent of T-cell depletion are the main mechanism that explains the increased susceptibility of these patients to opportunistic infections [56, 57]. Also, HIV decreases the circulating pool of effector and memory CD8+ T-cells that are able to combat viral infection with a final goal to enable CD8+ T-cell function [58]. In HIV patients, the depletion of T cells and their impaired activity are associated with lower level of cytokines such as IFN-γ and TNF-α that allow progressive disseminated histoplasmosis with increased fungal burden and mortality [44].

Macrophages resist HIV-1 infection much better than CD4+ T cells [59], but they have impaired activity against H. capsulatum [18, 44]. They bind fewer yeasts than cells from uninfected individuals as the HIV glycoprotein 120 envelope is responsible for this inhibition. A direct correlation is described between the CD4+ T-cell count and the capacity of macrophages to bind yeast cells. Once engulfed, yeasts grow more rapidly within macrophages from HIV-infected persons than in non-infected [44], and macrophages are not able to perform de second part of their defense in order to destroy H. capsulatum [60]. With a default immune response, macrophages cannot sterilize the infection, and dormant fungi from granuloma will be prone to reactivate.

The common histopathologic profile in HIV/AIDS co-infected patients with H. capsulatum is lack of organized inflammatory response with massive influx of macrophages and scarce number of lymphocytes. Thus, well-defined granulomas are infrequently present [61].

4. Clinical manifestations of H. capsulatum in HIV-infected patients

For primary histoplasmosis, the forms of disease depend on the degree of host immunosuppression and the yeast inoculum. Persons with higher CD4 + T-cell count, under cART, exposed to H. capsulatum could have no symptoms or develop an acute mild form of illness more often not recognized if the patients are not living in an endemic area. In this type of patients, the disease is restricted to the lungs as in general population but occurs in less than 5% of the cases [18]. On the opposite side, HIV-infected patients with scarce immunity (CD4 counts < 150 cells/mm^3) and not taking ART to develop progressive disseminated histoplasmosis. This is the most common profile of histoplasmosis, described in up to 95% of cases [62]. This pathway is common to exogenously acquired histoplasmosis as well as to reactivation and is determined by the hematogenous dissemination through the reticuloendothelial system (RES) that is containing parasitized macrophages. The term PDH describes the constant growth of organism in multiple organs rich in mononuclear phagocytes after the yeasts migrate from the lungs [45]. In endemic area, it is impossible to differentiate the reinfection to reactivation of dormant endogenous foci. Due to defective T-cell immunity in AIDS, reactivation seems to be the common pathway to histoplasmosis; however, autopsies series performed in the 1950s showed that although H. capsulatum is present in the lymph nodes, the cultures performed from these sites were sterile [45]. Thus, in endemic areas this evidence supports reinfection or progression of unrecognized histoplasmosis.

Depending on the degree involvement of RES and the underlying immune condition, different types of infection have been described. The acute disseminated form in AIDS patients is characterized by a high degree of RES involvement with closely packed macrophages engorged with yeast form [63] and have severe clinical implication as sepsis-like syndrome with septic shock, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation, neurological, hepatic, and renal involvement. Several cases of reactive hemophagocytic syndrome have been described [64] with bone marrow biopsy demonstrating the presence of histiocytes phagocytosing erythrocytes with poor outcome. Fever, weight loss, lymphadenopathy, hepatosplenomegaly, vomiting, and diarrhea are present as liver, spleen, bone marrow, and gastrointestinal tracts are the most commonly involved sites. Oropharyngeal and gastrointestinal mucosal ulcers are rarely present [63], but cutaneous lesions are described especially in Latin American late-diagnosed cases (66% versus up to 10% in the United States) [65]. The biopsy from cutaneous lesions (multiple disseminated papules, plaques, nodules, and pustules) could provide a simple and rapid diagnosis showing H. capsulatum yeasts intra- and extracellularly. CNS involvements such as encephalopathy, acute meningitis, or encephalitis are demonstrated in acute aggressive form of DPH with poor outcome [66]. Other atypical manifestations are described in acute form as chorioretinitis, colonic masses or anal ulcers, and pericarditis [45]. Acute disseminated forms rapidly evolve to death if untreated; therefore, rapid diagnosis and initiation of intravenous fungicidal therapy are required.

The second form of manifestation is subacute disseminated histoplasmosis, with a moderate involvement of the RES and also a moderate degree of macrophages parasitization [63]. Subacute or intermediate form is correlated with a longer interval of time when symptoms are present, in consequence a later presentation in the medical system. Manifestations are related to the development of focal lesions in various organs and associate with fever, weight loss, and weakness. Almost 25% of the patients have focal lesions in different organ systems, including gastrointestinal tract, endovascular, CNS, and adrenal glands [45, 63]. Gastrointestinal tract is commonly

affected in subacute form, in addition to hepatic and splenic involvement. Lesions could be observed from the oropharynx to anus [67], but autopsies series demonstrate that the most affected parts are the colon and cecum followed by the terminal ileum with unique or multiple, deep, or diffuse ulcerations that lead to perforation or strictures, polypoid, and nodular masses that are complicated with obstruction. Symptoms frequently present in AIDS patients are: diarrhea, crampy abdominal pain, and tenderness in association with fever. Ascites, lower intestinal bleeding, and intestinal obstruction of the ileum are rare. In case of severe diarrhea, signs of malabsorption are present. Endoscopic examination especially of the right colon with subsequent biopsies could establish the diagnostic of PDH and exclude other AIDS-associated opportunistic infections (gastrointestinal tuberculosis and CVM colitis), cancers (Kaposi sarcoma and adenocarcinoma), idiopathic inflammatory bowel disease (ulcerative colitis and Crohn disease), and sarcoidosis. Systematic colonic biopsies must be performed in HIV-seropositive patients who have unexplained GI tract pathology because it can establish diagnosis in up to 89% of cases [68].

Endovascular forms of subacute PDH are represented by endocarditis on native or prosthetic valves, infection of abdominal aortic aneurysms, or prosthetic vascular grafts. These manifestations are rare, but in HIV patients who develop embolic phenomena in context of negative blood culture and extended vegetations on the left-sided valves (aortic valve), clinician must consider histoplasmosis.

Central nervous system (CNS) is involved in subacute PDH under several forms: subacute or chronic meningitis, diffuse encephalitis, cerebritis, focal granulomatosis lesions of the brain or spinal cord, and stroke due to fungi emboli [69, 70]. The CNS involvement in PDH is rare and the most common form is basal meningitis, even meningeal syndrome is described in less than 10% of these patients. Four classical forms of CNS histoplasmosis have been described, three of them in subacute form: isolated subacute or chronic meningitis, subacute or chronic form that associates other localizations (liver, lymphatic nodes, mucocutaneous, etc.), and focal lesions in the brain or histoplasmoma [71]. CNS symptoms during PDH have a slow progression starting with headache, confusion, and altered sensorium followed in weeks by seizures, ataxia, and focal deficits. Similar to tuberculosis, basilar meninges are affected, thus oculomotor nerves II, IV and VI are involved with cranial nerve palsy. In evolution, hydrocephalus could appear that requests neurosurgical evaluation for insertion of a shunt after few weeks of antifungal treatment [70]. The cerebrospinal fluid (CSF) is clear with pleocytosis (between 10 and 100 cells and the predominance of lymphocytes), elevated protein level, and hypoglycorrhachia in up to 80% of the patients. Direct examination of CSF is frequently negative, but culture could confirm histoplasmosis if the quantity and the time of growth are sufficient (several weeks are needed with the delay of the diagnosis). In subacute form of PDH in HIV-infected patients, due to the lack of antibodies in CSF correlated with the immunosuppression grade; this test is positive in less than 70% of the cases but Ag detection could provide a positive result in more than 90% of the cases [71]. Still, no technique is validated for detection of Histoplasma capsulatum antigen in CSF, this test being available only for urine samples. Histoplasmoma determines mass effect and the computer tomography scan detects ring enhancement with the administration of contrast, like in abscesses (toxoplasmosis) or malignancies [62]. The stereotactic brain biopsy is needed, and the result confirms the diagnosis as yeasts are detected in the caseous center of the granulomas [72].

Autopsy series have described others lesions as every single organ can be affected in subacute form of PDF. The involvement of adrenal glands has been reported in up to 80% of the cases although symptoms are rarely present and most of the time

as unique manifestation [73]. At the gross examination, both adrenals are enlarged, which corresponded with the previously CT images performed. Focal areas containing parasitized macrophages can be found in both medulla and cortex. In severe infection, diffuse infiltration in parenchyma led to the destruction of both adrenal glands. Four categories of histopathological lesions have been described that are correlated with the host reaction against Histoplasma capsulatum: tuberculoid, anergic, mixed, and sequelae [74]. Adisson's disease with fever, malaise, nausea, vomiting, orthostatic hypotension, hyponatremia, and hyperkalemia occur in less than 10% of patients when extensive lesions have destroyed both adrenal glands.

Chronic progressive disseminated histoplasmosis is the third syndrome with the mildest RES involvement but also with the mildest macrophages parasitization [63], and is characterized by mildest and prolonged manifestation during years, occasionally intermittent and it is described only in adult people. Constitutional symptoms such as fatigue, weakness, gradual weight loss, malaise, lethargy, and low-grade fever are intermittently present. The pathognomonic sign is oropharyngeal ulcerations that are well delimited, deep, and painless. All the mucosal areas could be involved: oral cavity, lips, tongue, pharynx, nasal septum, larynx, labia, or penis. Biopsies performed for single lesions to exclude oral squamous carcinoma indicate granulomas with macrophages containing yeasts, but simple MGG-stained smears (May-Grunwald-Giemsa) or periodic acid-Schiff stains are useful to visualize Histoplasma capsulatum. Hepatosplenomegaly is present in almost a third of the patients, and in few cases, chronic granulomatous hepatitis has been described [75]. Chronic meningitis appears as single manifestation of the disease [45], in contrast to the subacute form where multiple organs are involved. Endocarditis, bone infection (septic arthritis and osteomyelitis), Addison disease, and pancytopenia caused by bone marrow suppression have been cited in literature as uncommon. Not recognized and treated, chronic PDH progresses to death.

Another distinct form is immune reconstitution inflammatory syndrome (IRIS) as a complication of starting cART in HIV-infected patients when a decay greater than 1 log in viral load associates inflammatory and atypical clinical features with signs and symptoms unexplained by a newly acquired infection or treatment failure [75, 76]. Both forms have been described as the immune system begins to recover following treatment: "unmasking" IRIS (flare-up of an underlying and previously undiagnosed histoplasmosis) and "paradoxical" IRIS (flare-up of a previously treated histoplasmosis). Compared to other pathogens, the incidence of histoplasmosis-associated IRIS is low (0.74 cases at 1000 HIV-infected person-years) and remain stable during the last 20 years in French Guyana where histoplasmosis is the most frequent opportunistic infection in HIV [76]. The clinical findings are polymorphic as in disseminated form with fever, lymph node enlargement, digestive, hematologic, respiratory, mucocutaneous manifestations and less frequent neurological, rheumatological, or ocular involvement [76].

Some clinical differences have been noted between the two variants, especially in Africa where H. capsulatum var. capsulatum coexists with H. capsulatum var. duboisii and HIV-epidemic remain the main health problem in the last decades. Due to the tropism of the variety duboisii for lymph nodes, skin, and bones, in HIV-infected patients, the dissemination of this yeast associates with classical PDH ulcers, nodules, psoriasis plaque, subcutaneous nodules, osteolytic lesions in the skull, ribs, vertebrae and enlarged lymph nodes [4].

Co-infections with other opportunistic infections have been described, due to the immunocompromised status of HIV-infected patients. In countries from Latin-America, the percentage of triple infections is very high: Columbia (51%), Brazil (43%), Argentina (42%), French Guyana (37–42%), and Panama (25%) [77].

The most reported is association with tuberculosis as this is the leading opportunistic infection related to HIV [77–80]. Both are able to spread and determine miliary forms and granuloma formation. The overlapping symptoms can delay the final and complete diagnosis. In this context, constitutional signs are frequently present with respiratory symptoms in only half of the patients despite that chest X-rays reveal infiltrates of the lungs [78]. Other common clinical findings associated with fever are: lymphadenopathy, hepatomegaly, splenomegaly, gastrointestinal pain, abnormal liver function tests, anemia, leukopenia, and thrombocytopenia [79]. If tuberculosis diagnosis is rapid by direct microscopic observation of acid-fast-bacilli (AFB), the histoplasmosis diagnosis confirmation is more difficult, primarily by histopathology if the patient is not living in an endemic area. Blood and bone marrow culture are useful to diagnose both disseminated diseases [79]. Co-occurrence of TB/histoplasmosis disseminated infections must be suspected by the persistence of the symptoms after completion of anti-Koch's regimen in patients with confirmed TB; thus, H. capsulatum must be tested from different specimens [80].

Other opportunistic infections (OI's) associated with histoplasmosis-HIV coinfection have been described: pneumocystosis [81], cryptococcal infection [82], cytomegalovirus infection, Salmonella infection, candidiasis, and toxoplasmosis [75]. Sometimes, more co-infections could be hosted by the same HIV-infected person [83]. As all of them are associated with severe immunodepression and have non-specific clinical signs and symptoms, clinicians must by aware of these possibilities and investigate in order to confirm the diagnostic and to provide appropriate treatment.

5. Diagnosis

In non-endemic areas where clinicians and pathologists are not aware of this pathology, the diagnostic of histoplasmosis in HIV-infected patients is difficult due to the unspecific symptoms in progressive disseminated form. For clinicians, it is important to remember that even short exposure in endemic area should be a reason to consider histoplasmosis in HIV-infected patients, as early and rapid diagnosis followed by initiation of optimal treatment is able to improve survival.

In April 2020, WHO released a set of recommendations for the management of histoplasmosis among PLWHIV [1], which contain guidelines for the diagnosis and treatment with the aim to provide the same approach for the entire health system, not only for the countries that face the highest burden as North America, Central America, South America, and some countries from Asia and Africa.

According these guidelines, "test and treat" concept for detecting and treating all HIV-infected persons is the most important strategy as this reduce the number of opportunistic infections, including histoplasmosis. Further, among people living with HIV, "disseminated histoplasmosis should be diagnosed by detecting circulating Histoplasma antigen" on the basis that:

- Traditional gold standard (culture from peripheral blood or tissue specimens, histopathologic analysis, and special stains) is based on conventional laboratory tests that have their limitations in terms of time and performance, imposing Biosafety Level 3 Laboratory infrastructures with trained personnel;

- Serodiagnosis tests that detect the presence of antibodies against Histoplasma capsulatum have decreased sensibility in immunosuppressed patients and are

not able to differentiate the active from past infection; also, they cross-react with other antigens from Coccidioides, Paracoccidioides, or Blastomyces;

- Molecular testing of DNA detection has high accuracy but there is a lack of consensus, technique, and availability of kits;

- Antigen detection assays are the most accurate to diagnose progressive disseminated histoplasmosis in HIV-infected persons. These tests are available, affordable, and can be performed in all laboratories (Biosafety Level 1 and 2) from non-invasive samples (urine) and reduce the time to diagnosis.

Urine antigen detection test is more sensitive than the serum antigen test for AIDS patients with disseminated histoplasmosis. Different publications showed that 92–100% of patients have antigenuria compared to almost 50–92.3% who present antigenemia [64, 84] depending on the type of assay. False-positive results in testing urinary antigen assay could appear in other mycoses as Blastomyces dermatitidis, Talaromyces marneffey, and Paracoccidioides brasiliensis because they have the same class of cell wall galactomannan, but not in aspergillosis [84]. In transplant recipients who received thymoglobulin or in cases associated with the presence of rheumatoid factor, the Histoplasma serum antigen could be false positive, and thus, urinary Ag is required [64].

Antigen detection is an important tool for monitoring the therapeutic response. In case of persistent antigenuria with failure to decrease after 1 month of treatment an ongoing infection is present [85]; meanwhile, increased titers should advise about the possibility of relapse [86]. For CNS histoplasmosis, antigen detection is a reliable to orientate the diagnosis as this becomes positive in less than one week combined with detection of antibodies from CSF and serum, as culture requires more than 2 weeks for growth [87].

However, the investigation of an HIV-infected person must be comprehensive, in order to evaluate the immune status of the patient and the extension of the disease. Also, other co-infection must be ruled out. Some unspecific biological abnormalities could indicate PDH as adjunct laboratory markers: very high level of serum lactate dehydrogenase (>600 UI/ml) [88], increased level of ferritin (>1000 ng/ml) [45, 89], increased AST level associated with increased alkaline phosphate and thrombocytopenia [88, 90], and hematuria and proteinuria [90].

6. Treatment

Patients with CD4 count > 300 cells/mm^3 who develop acute pulmonary histoplasmosis must be treated as immunocompetent persons [91].

Progressive disseminated histoplasmosis in HIV-infected patients is a life-threatening infection that requires always treatment, as the mortality rate in untreated infection is very high (up to 100%) [91].

Several guidelines have been released with recommendations for treatment for disseminated form of histoplasmosis in people living with HIV: IDSA, DHHS, EACS, WHO. According to the last one published in 2020, the treatment is related to the form of the infection considering that:

-Severe and moderate-severe form is defined as the presence of at least one symptom or sign that involved vital organs and with a general alteration of WHO

performance status more than 2; mild and mild-to-moderate form have no symptoms or signs listed before;

-cART should be initiated as soon as possible if histoplasmosis CNS involvement is not suspected or proven as this poses additional challenges and requires different approach than the other forms [1].

The preferred regimen for severe or moderate-severe form as induction therapy is intravenous liposomal amphotericin B (3 mg/kg/day) for up to two weeks, as this formulation has demonstrated better outcomes than standard deoxycholate formulation in terms of rapid and complete response (82% versus 56%), lower mortality (2% versus 13%), and nephrotoxicity (9% versus 37%) [92]. Clinical improvement (resolution of fever and no need for ventilatory support, or vasopressors) must be followed by step-down therapy to itraconazole 200 mg three times a day for 3 days, and then 200 mg twice a day for at least 12 months as maintenance treatment [1, 91, 93].

If liposomal formulation is not available, standard deoxycholate amphotericin B must be initiated in dose of 0.7–1.0 mg/kg/day with close monitoring of the renal function and electrolytes. Dose reduction or rapid switch to itraconazole is needed if the patient develops nephrotoxicity despite proactive fluids and electrolytes replacement or other toxicities (anemia and toxic-related infusion).

Intravenous amphotericin B lipid complex at 5 mg/kg/day is an alternative option but it demonstrated a lower efficacy than two previous options [18] in AIDS patients with PDH.

Itraconazole is preferred for induction and maintenance therapy for mild or mild to moderate forms of histoplasmosis in HIV-infected patients. After 3 days of 200 mg three times a day as loading dose, 200 mg twice a day must be continued for at least 12 months, with dose adjustment based on drug-drug interaction with ARV and itraconazole serum concentration [1, 91, 93]. Itraconazole must be administrated with food or low-pH beverages (such as cola) in order to increase absorption. Liquid itraconazole is preferred due to better absorption if it is well tolerated. Blood level must be measured after 2 weeks of treatment (time to reach steady state) to verify if achieving optimal concentration between 1 and 2 mcg/ml. Serum concentrations could be useful in case of drug-drug interactions or to assess the adherence of the patient. Higher concentration (>15 mcg/ml) is correlated with toxicities. Most adverse events in HIV-infected patients are nausea, vomiting, rash, and pedal edema.

Like all the triazoles, itraconazole exhibits multiple drug interactions, most notably with cytochrome P450-inducing drugs [94]. Before starting treatment, these potential drug-drug interactions must be evaluated as HIV infection must be treated as well. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as Efavirenz (EFV), Nevirapine (NVP), and Etravirine (ETR) reduce itraconazole blood level; meanwhile, Doravirine (DOR) display only low interactions and co-administration does not require TDM for itraconazole like for previous ones. Boosted protease inhibitors (PIs) such as lopinavir (LPV/r), atazanavir (ATZ/r), darunavir (DRV/r or DRV/c) increase itraconazole blood level so must be avoided or TDM is needed to avoid toxicities. Integrase inhibitors (INSTI) such as Raltegravir or Dolutegravir have no interaction so are safe to prescribe them in association with itraconazole but, due to cobicistat, Elvitegravir will increase itraconazole level [95] and must be avoided. Tuberculosis medication's rifampicin and rifabutin, potent inducers of cytochrome P450 (CYP) enzymes and transporters, decrease the level of itraconazole; on the other hand, itraconazole may increase the blood levels of rifabutin [94, 95].

If itraconazole cannot be administrated, alternative therapy must be considered for treating less severe disseminated disease. Posaconazole is the preferred antifungal

for treating H. capsulatum as it demonstrates high efficacy in patients who failed other fungicidal medication [96]. Posaconazole treatment duration ranged from 6 weeks to 48 weeks depending on the clinical form and was followed by successful clinical outcomes [97]. Serum level must be measured after 5 days in order to reach steady state to determine if the drug has adequate absorption (concentration must be >1 mcg/mL). Fluconazole 800 mg once daily is associated with a slower decline of antigenuria than itraconazole [98] and with a higher rate of resistance emergence in HIV-infected patients due to a single point mutation [99], so is no longer recommended as maintenance therapy [100]. Voriconazole was associated with increased mortality in the first 42 days when compared to itraconazole in a retrospective cohort in which have been included 24.7% HIV-infected patients with disseminated histoplasmosis [101]. Isavuconazole could be an alternative to Posaconazole and cases have been published with good outcome [102], but there are not enough data to generate a conclusion.

The maintenance therapy with itraconazole in AIDS-associated disseminated histoplasmosis must be 12 months in order to suppress residual infection and to prevent relapses. Is safe to discontinue itraconazole after 12 months when CNS involvement is absent, CD4 counts are more than 150 cells/mm^3, HIV-RNA is suppressed under cART, and Histoplasma antigenuria is less than 2 ng/mL [35], otherwise must be continued with 200 mg/day for the entire life as long-term suppressive therapy [91, 93]. In some cases, itraconazole can be replaced by Posaconazole XR 300 mg/day (best option), Fluconazole 400 mg/day, or Voriconazole 200 mg/day.

A special approach must be considered for H. capsulatum meningitis. The induction therapy with intravenous liposomal amphotericin B 5 mg/kg/day must be longer, for 4–6 weeks, followed by itraconazole 200 mg two or three times a day for more than 12 months with dosage adjusted not to exceed 10 mcg/mL [91, 93]. The maintenance treatment with Itraconazole must be continued till the resolution of CNS abnormal findings with negative antigen and culture of CSF when CD4 count recovered as HIV viral load became undetectable. Itraconazole could be replaced in case of intolerance by Posaconazole as alternative best option, Fluconazole, or Voriconazole.

All guidelines recommend monitoring treatment response by performing antigen level at the initiation of antifungal medication; at the end of amphotericin B induction phase, at 3, 6, and 12 months and when it is decided the cessation of therapy [1, 91, 93]. Any increase in antigen level must be followed by a comprehensive evaluation considering adherence to antifungal and ARV treatment. TDM for itraconazole level is required, and also CD4 count and HIV-RNA determination as relapses are related to non-adherence [35].

Antiretroviral therapy should be initiated as soon as possible if CNS involvement is not suspected or confirmed [1, 91]. In order to avoid drug-drug interaction with any triazole, INSTI-based regimen (DTG or RAL) are preferred as first-line therapy or doravirine (DOR) as NNRTI-based regimen. Immune reconstitution inflammatory syndrome (IRIS) is uncommon in HIV-infected people with histoplasmosis with an incidence rate of 0.74 cases/1000 HIV-infected person-years [76]; thus, the cART should not be delayed. The management of IRIS associated with histoplasmosis is to continue antiretroviral treatment as well as antifungal therapy with short term of oral steroids associated (Prednison 1 mg/kg per day) if there are life-threatening complications. If patient is naïve to cART, a two-week delay is recommended before starting medication; meanwhile, induction antifungal therapy is in place.

The most challenging situation for clinicians is treatment of histoplasmosis/tuberculosis co-occurrence in HIV-infected patients as currently, there are no guidelines or recommendations targeting all three infections. Tuberculosis must be

treated according WHO, DHHS, EACS guidelines, but due to drug-drug interactions, especially in HIV heavily pretreated patients requiring protease inhibitors regimens or in case of MDR-tuberculosis, clinicians must seek experts advise. Due to drug-drug interactions between itraconazole—rifampin or rifabutin—some ARV drugs, TDM for itraconazole must be perform on a regular basis. Results from a case series study conducted in Columbia on 12 PLHIV determined investigators to recommend fluoroquinolone instead of rifampicin use for TB as three patients treated with rifampicin had undetectable levels of itraconazole [78]. Another challenge is delaying initiation of ARV therapy up to 14 days as CD4 count is frequent less than 200 cells/mm^3, due to the associated risk of developing IRIS [76].

7. Preventing exposure

HIV-infected persons with CD4 count <150 cells/mm^3 should avoid activities associated with high risk for histoplasmosis: cleaning chicken coops, disturbing area contaminate with bird or bat droppings, exploring caves, demolishing old buildings, and creating dust as they are working with surface soil [91, 93].

8. Primary prophylaxis

In high endemic areas (incidence >10 cases/100 patients-years), primary prophylaxis with Itraconazole 200 mg daily in HIV-infected patients with severe immunodepression reduce the frequency but not the mortality due to histoplasmosis [103], and thus is recommended for patients with CD4 count <150 cells/mm with high risk due to occupational exposure. The primary prophylaxis must be discontinued if the immune status is improving when CD4 counts attaint 150 cells/mm^3 and remain stable for more than 6 months, and must be restarted when CD4 count decreases <150 cells/mm [93].

9. Conclusions

Histoplasmosis overlapping HIV-pandemic redefined the epidemiology and the clinical features of this disease, generating a particular form in AIDS: progressive disseminated histoplasmosis. Challenges in diagnosis (especially in non-endemic areas where a significant knowledge gap still exists), treatment (due to drug-drug interactions between fungicidal drugs and cART, and availability of medications) and association with other opportunistic infections (especially tuberculosis) have determined specialists to release guidelines but also research priorities. Hopefully, access to antiretroviral medication for all HIV patients will change the face of this pathology till new strategies will be available in order to control this potentially life-threatening illness.

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