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CASE REPORT

Disseminated histoplasmosis: case report and review of the literature

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ABSTRACT

Case report: We report the case of a young Cameroonian woman who presented with cough, hyperthermia, weight loss, pancytopenia, and hepatosplenomegaly. A positive HIV serology was discovered and a chest radiography revealed a 'miliary pattern'. Bone marrow aspiration pointed out yeast inclusions within macrophages. Given the morphological aspect, the clinical presentation and immunosuppression, histoplasmosis was retained as a working hypothesis. Antiretroviral and amphotericin B treatments were promptly initiated.

Review: Given the immigration wave that Europe is currently experiencing, we think it is important to share experience and knowledge, especially in non-endemic areas such as Europe, where clinicians are not used to face this disease. Histoplasmosis is due to *Histoplasma capsulatum var. capsulatum*, a dimorphic fungus. Infection occurs by inhaling spores contained in soils contaminated by bat or bird droppings. The clinical presentation depends on the immune status of the host and the importance of inoculum, varying from asymptomatic to disseminated forms. AIDS patients are particularly susceptible to develop a severe disease. Antigen detection, molecular biology techniques, and microscopic examination are used to make a rapid diagnosis. However, antigen detection is not available in Europe and diagnosis needs a strong clinical suspicion in non-endemic areas. Because of suggestive imagery, clinicians might focus on tuberculosis. Our case illustrates the need for clinicians to take histoplasmosis in the differential diagnosis, depending on the context and the patient's past history.

KEYWORDS
Histoplasmosis; Pancytopenia; AIDS; Dimorphic fungus; Histoplasma capsulatum

Case report

A 37-year-old woman presented at the emergency department with following complaints: hyperthermia, cough for 15 days, weight loss and impairment of her general condition. The patient is of Cameroonian origin and arrived illegally in Belgium, which could possibly explain her late presentation to the hospital.

The first laboratory results revealed severe pancytopenia (hemoglobin = 3.9 g/dL, platelets = 30,000/mm^3, white blood cells = 2750/mm^3) and an inflammatory syndrome with a C-reactive protein up to 180 mg/L. Among abnormal lab results, lactate dehydrogenase = 1522 U/L and ferritin = 9074 µg/L were particularly elevated. Liver enzymes were normal except for aspartate aminotransferase which was slightly elevated at 116 U/L. A positive HIV-serology and a lymphocytic typing revealed an immunosuppression compatible with AIDS (CD4 + T-lymphocyte count = 0/mm^3; HIV-1 viral load = 5.3 log copies/mL). Kidney function was normal, with creatinin = 0.69 mg/dL. Ultrasound examination showed hepatosplenomegaly associated with a mild peritoneal effusion. Bone marrow aspiration pointed out a pronounced dysplasia on red cells lineage and, above all, it highlighted a significant amount of intracytoplasmic inclusions within macrophages (Figures 1 and 2). At that time, bone marrow was also plated on Sabouraud agar medium with antibiotics (*bioMérieux, France*) and blood agar medium (*Trypcase Soy agar + 5% sheep blood TSS, bioMérieux*).

Among the differential diagnoses, leishmaniasis, histoplasmosis, and other yeast infections were most considered. Given the morphological aspect, the clinical presentation and the immunosuppression, histoplasmosis was retained as a working hypothesis. The suspected causal species would hence be *Histoplasma capsulatum var. capsulatum*. Periodic Acid Schiff (PAS) staining was performed to strengthen this assumption (Figure 3).

A bone marrow biopsy was also performed and the pathologist observed the same inclusions inside histiocytes with hematoxylin and eosin (H&E) (Figure 4) and Grocott methenamine silver (GMS) (Figure 5) stainings.

Positivity with both PAS and GMS stainings, as well as specific *Leishmania* polymerase chain reaction (PCR) performed in the Institute of Tropical Medicine (ITM) (Antwerp, Belgium) on bone marrow allowed to exclude Leishmaniasis, one of the major differential diagnosis.

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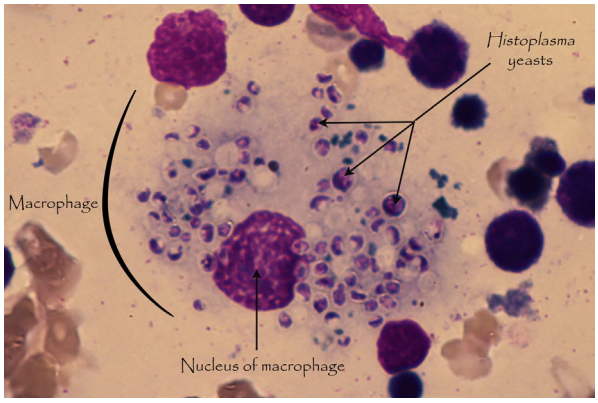

Figure 1. Bone marrow aspiration stained by May-Grünwald Giemsa: Histoplasma yeasts inside a macrophage.

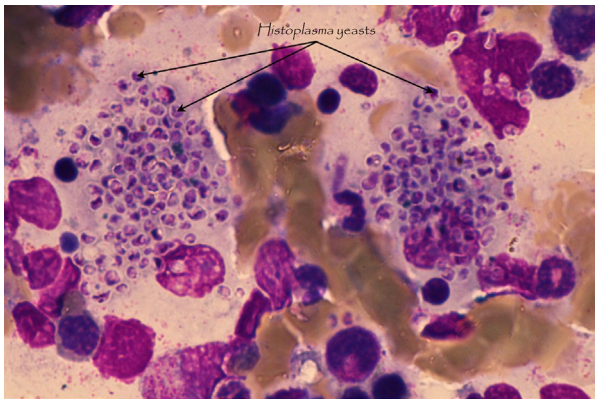

Figure 2. Bone marrow aspiration stained by May-Grünwald Giemsa: numerous intracytoplasmic Histoplasma yeasts viewable into macrophages.

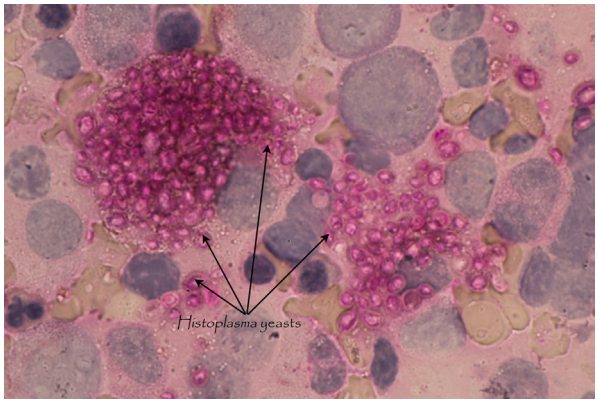

Figure 3. Bone marrow aspiration stained by Periodic Acid Schiff: Histoplasma yeasts inside macrophages.

Radiography of the chest revealed a 'military pattern' as seen in tuberculosis, also compatible with histoplasmosis. In order to exclude the possibility of a co-infection, *Mycobacterium tuberculosis* culture, direct examination (auramine stain, *RAL Diagnostics*), and PCR *(Mycobacterium tuberculosis complex, in-house real-time PCR)* were performed on sputum, lung aspiration and cerebrospinal fluid (CSF). Results returned negative. Cerebrospinal fluid examination and magnetic resonance imaging did not show any signs of cerebral infection. Given her HIV-positivity with extreme immunodeficiency, treatment with highly active antiretroviral treatment (Raltegravir, Abacavir, Darunavir, Ritonavir, Lamivudine) as well as amphotericin B (3 mg/kg daily, liposomal complex) was started immediately.

Subsequently, inclusions also emerged inside neutrophils on peripheral blood smears (Figure 6) and became increasingly numerous before to progressively disappear. It is interesting to note that despite the fact yeasts were visible on blood smears, blood culture bottles (*Bact/Alert® SA and FN Culture Media, Biomérieux*) remained negative even after a prolonged incubation time to 21 days. Although composition of the medium might reasonably be questioned, as bottles are not specifically designed for *Histoplasma* growth, this could also be explained by intracellular parasitism: the bottles used did not contain lytic agent. According to the literature, a lysis-centrifugation method or incubation of bottles containing lytic agent would probably have increased sensitivity [1–3].

Unstained bone marrow slides, EDTA-blood and later on, a yeast culture were sent to the national reference center for Mycosis (NRC) at the University Hospital of Liège (CHU Liège) to perform ITS sequencing of ribosomal fungal RNA genes. All samples revealed the presence of Histoplasma capsulatum DNA (Gen BANK n°1970915) with 100% homology with reference database. Using a different molecular biology technique (*in house real-time Histoplasma specific PCR*), ITM also confirmed the identification of *Histoplasma capsulatum* species on bone marrow and blood samples. However, it was not possible to reach the variety level with none of these two approaches.

Histoplasma yeast form grew after 10 days at 37 °C on blood agar medium (*Trypcase Soy agar + 5% sheep blood TSS, bioMérieux*) whereas Sabouraud medium remained sterile after two weeks of incubation. A GRAM stain was carried out and culture was sent for PCR confirmation. An identification by MALDI-TOF MS (Matrix Assisted Laser Desorption/Ionization – Time Of Flight) technology is attempted on Microflex® (Bruker Daltonics) device but Histoplasma's spectrum is not present in the database, so identification is not yet possible.

Despite optimal treatment, the patient developed a septic shock with multiorgan failure and disseminated intravascular coagulation. The patient died 13 days after admission.

Review of the literature

Introduction

Histoplasmosis is an opportunistic mycotic infection caused by *Histoplasma capsulatum*. There are two different varieties, *var. duboisii and var. capsulatum*, which differ from each other by epidemiology, clinical

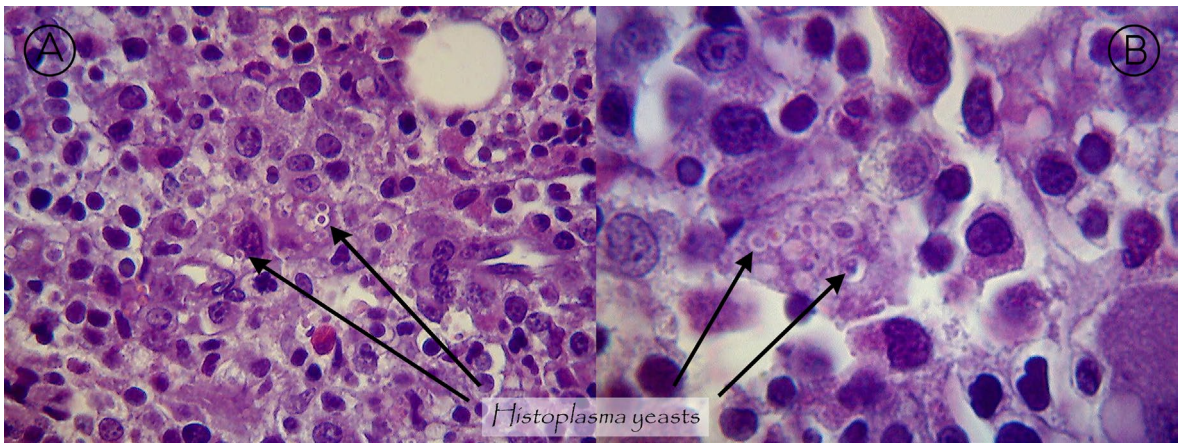

Figure 4. (A) (400×) and (B) (1000×). Bone marrow biopsy stained by H&E: Histoplasma yeasts inside macrophages.

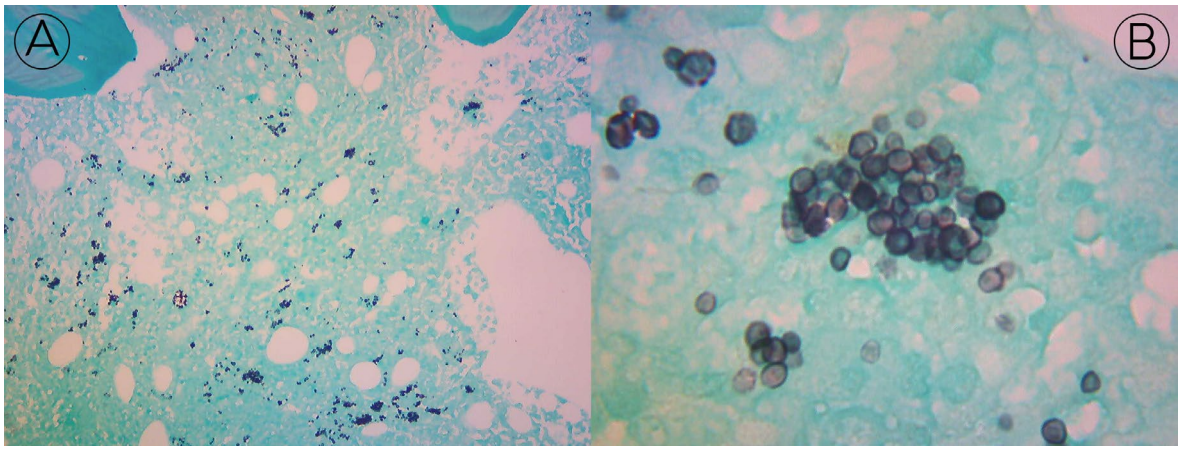

Figure 5. (A) (100×) and (B) (1000×). Bone marrow biopsy stained by GMS: Histoplasma yeasts.

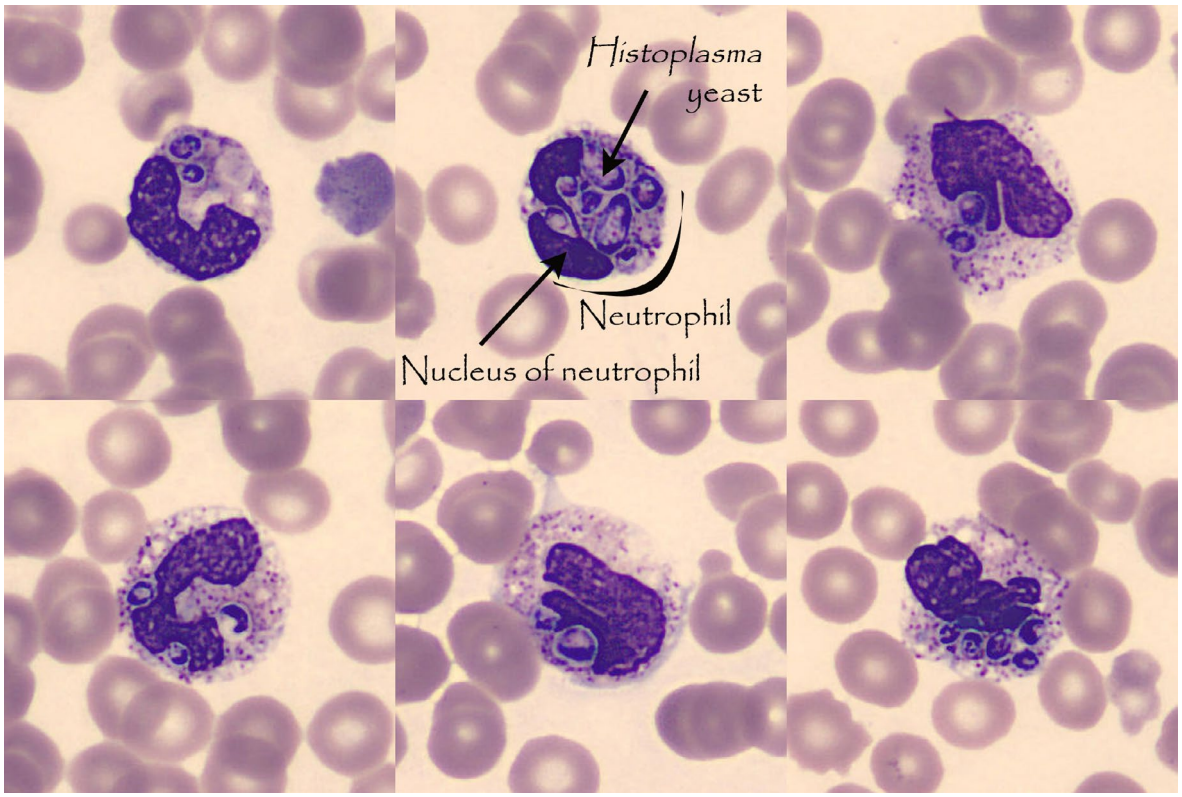

Figure 6. Blood smear stained by May-Grünwald Giemsa: Histoplasma yeasts inside neutrophils.

presentation, and morphological aspects. *Histoplasma capsulatum var. capsulatum* is the most frequent one and also more dangerous [4].

Epidemiology

Histoplasma capsulatum var. capsulatum is a dimorphic fungus. Its saprobic mold form grows in soils contaminated by bird and bat droppings. People are infected by inhaling microconidia, particularly in confined spaces such as caves, farms, silos, dovecotes, or chicken-farms. There is no interhuman transmission. Disease occurs worldwide and is highly prevalent in areas along the Mississippi and Ohio valleys of the USA and in Central and South Africa [5]. Europe only has a few endemic locations in a part of Italy (Emilia-Romagna area) [4] and in Germany, where the fungus has been found in the soil [6]. Most of the cases encountered in Europe are imported through immigration, from people often co-infected with HIV [5]. Disseminated histoplasmosis is a criterion for AIDS definition since 1987.

In the case we report, the patient came from Cameroon. A study recently conducted by a health center in the capital Yaounde showed that histoplasmosis is still widely underdiagnosed in Cameroon [7]. Fifty-six HIV-positive patients were recruited on the criteria of CD4 cells <200/mm^3, fever, chronic cough, weight loss, asthenia, and histoplasmosis-like skin manifestations. Histoplasmosis was detected in 13% of these patients, only based on positive direct examination (sputum, bronchoalveolar fluid, bronchial biopsy, skin biopsy) or culture results (sputum, bronchoalveolar fluid), which are not the most sensitive techniques. The authors concluded that histoplasmosis is an unknown public health problem in Cameroon that is often misdiagnosed as tuberculosis (TB) (7).

Physiopathology and clinical forms

Spores are inhaled and phagocytosed by alveolar macrophages which are first unable to kill the micro-organism [5]. *Histoplasma capsulatum* has developed several mechanisms to escape the immune system, allowing yeast cells to multiply into macrophages until they split up. Material from damaged yeast is then digested by dendritic cells and is presented as antigen to T-cells. CD4+ Th cells produce cytokines in response, which help to trigger oxidative burst inside infected macrophages. Epithelial cells of the lungs also play a role in neutrophil recruiting. Within 10–20 days, humoral immunity develops and primary lung lesions resolve [8–10].

Generally, cell-mediated immunity manages to control primary infection and people remain asymptomatic, or disease is limited to the lungs [4]. Radiology of the lungs usually reveals multiple focal granulomatous lesions with fibrosis and calcification [8]. More severe primary presentations are nonetheless described, mainly in HIV patients or in cases of massive inoculums in healthy hosts [5]. Given the important role of T-cells in host defense, it is easy to understand why patients with severely impaired immunity can develop a disseminated form in primary infection. Furthermore, even following activation of cell-mediated immunity, infection may not be completely cleared and latent Histoplasma ingested yeast-cells may persist [11]. Thus, when host immunity collapses, reactivation of the disease into the disseminated form can occur, sometimes several years after primary infection. Patients at risk are mainly HIV-infected individuals with CD4 T-lymhocytes count <150 cells/µl, organ transplant patients under immunosuppressive therapy [5] and individuals receiving cytokine-blocking therapies [11].

Different clinical forms are described:

The *primary acute pulmonary form* displays a flu-like picture with fever, cough, and dyspnea. The thoracic radiography usually shows uni- or bilateral lymphadenopathy, parenchymal infiltration and micro- or macronodules which will further calcify.

The *disseminated form* can occur several months, even some years, after the primitive form. It usually develops in immunocompromised patients, HIV positive individuals in particular. It is characterized by multiorgan damage, especially in the reticulo-endothelial system. Oropharyngeal ulcerations and involvement of adrenal glands are frequent [4,12]. Impairment of the central nervous system is not rare either. Cutaneous lesions, which can take many forms, occur more frequently in the AIDS population [13]. Approximately 30% of patients affected by disseminated histoplasmosis die from the infection [14]. Among these disseminated histoplasmosis, *fulminant forms* are also described. These forms are characterized by a septic shock with intravascular disseminated coagulation; multiorgan failure (kidneys, liver, lungs) and rhabdomyolysis, all of which may be associated with a hemophagocytic syndrome. Mortality of these severe cases is very high, up to 50–70% [15].

The *chronic pulmonary form* resembles tuberculosis with cough, hemoptysis, dyspnea, and the presence of cavities on chest X-ray. It progresses to respiratory failure and prognosis is poor [4].

In a few cases, *atypical presentations* are reported, such as brain abscesses in an immunocompetent adult [16] or endovascular infections [17].

Laboratory diagnosis

Antigen detection appears to be the most sensitive rapid assay, which detects *Histoplasma capsulatum* in the urine of 95% and the serum of 86% AIDS patients affected by disseminated histoplasmosis [18]. Several enzyme immunoassays (EIA) test for antigen detection exist. They can be performed on body fluids, especially urine and serum. They vary from each other by sensitivity, specificity, and possible cross-reactions with other fungal pathogens such as paracoccidiomycosis,

coccidioidiomycosis, and blastomycosis. The third generation *MVista® histoplasma QUANTITATIVE EIA antigen test* (*MiraVista diagnostics, USA*) is currently a good validated method for the diagnosis of histoplasmosis in HIV-infected patients. Nevertheless, this test is not commercialized and it is hardly used apart from the USA [15]. To make such a test available to resource-challenged countries, a similar Histoplasma antigen capture ELISA was developed at the Centers for Disease Control and Prevention (CDC). This test showed a sensitivity of 81% and a specificity of 95% in a cohort of AIDS patients in Guatemala [19]. A trial in Colombia also found that the antigen test successfully monitors the response to therapy [20]. Such antigen tests are not yet available in Europe. In view of its low predictive value in non-endemic areas, pre-test probability should be carefully assessed by clinicians.

PCR assay is a rapid, sensitive and specific method for diagnosing disseminated histoplasmosis but it is not yet standardized for routine use. It may be performed in specialized centers with in-house methods and may prove very useful. An alternative to *Histoplasma* specific PCR is a panfungal PCR followed by sequencing and targeting the ITS region of the fungal rRNA genes which can amplify the majority of fungal species. In the present case, this method was applied on bone marrow smears, EDTA-blood and yeast culture with the same results and led to the identification of *Histoplasma capsulatum* with 100% homology with the CBS mycological database [21]. However, it was not possible to reach the variety level. The D1–D2 region of 28S fungal DNA was also amplified but the same results were obtained. Other authors have reported the use of Multilocus sequence typing method for identification of *Histoplasma* complex at variety level [22] but this method was not considered due to the obvious morphologic aspect of the intracytoplasmic yeasts.

It is not uncommon for the diagnosis to be made by chance from microscopic examination, especially in non-endemic areas. Microscopy is simple, rapid, and cheap but sensitivity is less than 50% [23]. It can be applied to a large variety of samples including bronchoalveolar lavage, tissue biopsies, peripheral blood, or bone marrow aspiration. Smears are usually stained with May-Grünwald Giemsa and a search for yeasts inside macrophages is carried out. Small yeast cells (2–4 µm in length) are usually ovoid with budding on a narrow base at the smaller end. The yeasts reproduce within monocytes or macrophages and, when released, often remain in clusters. In Giemsa-stained preparations, a pale blue ring (the fungus cell wall) surrounds the darker blue cytoplasm that retracts from the wall, often giving the false impression of a capsule; the chromatin stains dark violet and appears as a crescent-shaped mass within the cell (Figures 1 and 2). A halo or pseudocapsule also appears with H&E, but the organism stains well and evenly with Gomori methenamine silver (GMS) or PAS (Figure 3) [24]. GMS and PAS both stain well structures containing a high proportion of carbohydrates molecules, such as cell walls of fungi. The first one stains structures in black and the second one gives magenta color. They allow differentiation between fungi and protozoa (*Leishmania spp.*). *Penicillium marneffei*, another dimorphic fungus, is also stained by GMS and PAS but its yeast-like forms show a characteristic intracytoplasmic transverse septum [25–27]. In some cases of severe disseminated histoplasmosis, accompanied by shock and multiorgan failure, routine peripheral smears may reveal yeast forms within circulating neutrophils [5,13].

Cultures can also be performed but require biosecurity precautions because of the risk of contamination for laboratory employees. The yeast phase is cultured at 35–37 °C on blood agar or Brain–heart infusion agar with cystein media and presents as smooth white to brown colonies [18]. This is the less contagious form but also the less distinctive one. The mold form is indeed more typical, with characteristic macroconidia. It grows at 25–30 °C within 1–6 weeks on Sabouraud's dextrose agar medium. The most contributive sample for culturing is bone marrow with a sensitivity of 70–90% [15] whereas global culture positivity is only met in 50–70% of cases [28]. For peripheral blood cultures, authors notably recommend the lysis-centrifugation technique, in order to increase sensitivity and to reduce the identification delay relative to other techniques [15]. Despite the fact that culture is considered as the gold standard to confirm diagnosis, time to obtain positivity is nonetheless too long in such life-threatening disease.

Serological methods based on specific antibody detection can be performed rapidly but usually give false negative results in AIDS patients (low sensitivity of 35%) [28]. A method based on complement fixation is slightly more sensitive but cross-reacts with other pathogens [29]. Furthermore, serology hardly discriminates active from passive infection. However, serology on CSF may be of interest for the diagnosis of neuromeningeal forms of histoplasmosis [15].

The histoplasmin skin test is a helpful tool for epidemiological purposes but cannot be used for diagnosis, as up to 80–90% of the population in endemic areas has a positive result [5].

In endemic areas where *Histoplasma* antigen detection is not available, another approach might be to use cross-reactivity of galactomannan antigen detection (Platelia™ Aspergillus enzyme detection, Biorad), commonly used for diagnosis of invasive aspergillosis. In non-endemic areas, usefulness of this method should be reassessed in light of lower prevalence [28].

Differential diagnosis

The differential diagnosis in HIV-infected individuals must include other opportunistic infections such as miliary tuberculosis (TB), disseminated cryptococcosis,

visceral leishmaniasis, and lymphoma [5]. *Penicillium marneffei* infection also has to be taken into account if the subject is coming from Southeast or Far Asia.

The first differential diagnosis to consider is tuberculosis. Histoplasmosis is still widely mistaken for tuberculosis [15]. The diagnosis of tuberculosis needs to be documented by culture and specific investigations. Moreover, when patients do not respond well to antituberculosis therapy, clinicians have to exclude histoplasmosis before considering multidrug resistant tuberculosis, especially in AIDS patients. It is also important to remember that a diagnosis of tuberculosis does not rule out a co-infection with histoplasmosis. In some countries, it is estimated that TB coinfection occurs in 8–15% of HIV-infected patients who have histoplasmosis [30].

Another variety of *Histoplasma capsulatum*, *Histoplasma capsulatum var. duboisii*, causes African histoplasmosis. The two varieties are genetically close but clinical and morphological features allow differentiation of these two diseases. Firstly, although lymph node, spleen, hepatic, pulmonary, or gastrointestinal lesions have also been described, African histoplasmosis usually involves skin, subcutaneous tissue and bones. Furthermore, yeasts in macrophages are much larger than those observed in the variety *capsulatum*: they are oval or lemon-shaped, thick walled and measure 8–15 µm long (vs. 5 µm at the maximum for *capsulatum* variety) [31]. Moreover, *H. capsulatum var. duboisii* infection is rarely found In HIV-positive patients [32]. Geographic distribution also plays a role for differentiation, as *duboisii* variety is only encountered on the African continent.

Differential diagnosis should also be made with other deep mycoses such as coccidiomycosis, paracoccidioidomycosis, and blastomycosis. These mycoses all have a similar pathogenesis, as the inoculum enters the host through the respiratory tract. They can all cause TB-like pulmonary lesions. Nonetheless, they differ in epidemiology and morphological aspects. PCR techniques may also prove very useful [6].

Treatment

Amphotericin B is considered as the antifungal of choice in case of moderate to severe disseminated histoplasmosis. To reduce its toxicity, lipid formulations can be used at the dose of 3 mg/kg daily (liposomal form) to 5 mg/kg daily (lipid complex). This is the best option in countries which can afford it. Itraconazole may be an alternative and even the primary choice in case of mild infections or for maintenance therapy [33].

Choice of treatment depends on the severity of the disease, the patient's immune status and the presence of CNS involvement. Itraconazole is never recommended for the treatment of patients with meningitis, regardless immune status [34].

In immunocompetent patients, mild disease with symptoms which does not last for more than four weeks does not require any treatment. If there is no improvement after one week, itraconazole should be started (200 mg, once daily, during 6–12 weeks). If infection is moderate or severe, lipid formulation of amphotericin B should be initiated for seven days, followed by itraconazole (200 mg, twice daily) to complete three months. Several criteria may help to define moderate to severe disease: body temperature > 39.5 °C, serum albumin < 3 g/dL, Karnofsky score < 60, liver enzymes > 5 times upper limit of normal, hypotension, systolic blood pressure < 90 mm Hg, hypoxia, mental status change, rhabdomyolysis, coagulopathy [34].

In immunocompromised patients (HIV infected/AIDS patients), lipid formulation of amphotericin B is recommended until clinical resolution [34]. Maintenance therapy is continued with itraconazole (200 mg twice daily) and may be lifelong necessary [33]. However, a multicenter study conducted in the United States has shown that discontinuation of antifungal therapy is safe in adherent patients who completed at least one year of antifungal treatment, and had CD4 counts > 150 cells/µL, HIV RNA < 400 copies/mL, Histoplasma antigenuria < 2 ng/mL and absence of CNS involvement [35].

When both amphotericin B and itraconazole are unavailable, fluconazole might be an alternative but is less effective and induces resistance during treatment [34].

Conclusion

In the case we reported, severe pancytopenia prompted clinicians to think about a hematologic disease and perform early a bone marrow aspiration which revealed intracellular parasitic yeast forms. Diagnosis of histoplasmosis was discussed soon after admission. This AIDS patient probably experienced a reactivation of latent histoplasmosis which can be suggested by the presence of calcified nodules on Chest X-ray.

In non-endemic areas, histoplasmosis is frequently revealed by direct microscopy but bone marrow is not always invaded and mucosal lesions may be absent. When direct microscopy does not suggest histoplasmosis, clinicians might logically focus on TB because of suggestive imagery, as TB is much more frequent than histoplasmosis. Our case illustrates the need for clinicians to take histoplasmosis in the differential diagnosis, depending on the clinical context and the patient's past history.

The availability of highly active antiretroviral therapy and lipid formulations of amphotericin B, the increased awareness of the problem by clinicians, and the development of rapid noninvasive diagnostic methods have led to a reduction of histoplasma-related mortality in endemic areas [15]. Mortality remains nonetheless high and low prevalence areas have to take up some challenges. In terms of diagnosis, detection of urinary

antigen is not currently available in Europe and PCR is only performed in specialized centers. Histoplasmosis may represent the first manifestation of AIDS in endemic areas [15]. Given the immigration wave that Europe is currently experiencing, practitioners will have to deal with uncommon and tropical diseases, in particular within the HIV-infected population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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