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BRIEF REPORT

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Disseminated histoplasmosis in an HIV-infected patient discovered by routine blood smear staining

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Histoplasma capsulatum is a dimorphic fungus of the *Ascomycetes* class. Histoplasmosis is the most common endemic mycosis in the USA and has emerged as an important opportunistic infection among patients with HIV living in or visiting endemic areas [1]. While the illness is subclinical or presents as a mild self-limited pulmonary infection in healthy individuals, the majority of cases involving AIDS patients show signs of a life-threatening disseminated infection. Presented here is a case of disseminated histoplasmosis in an HIV-infected patient living in Switzerland, which was diagnosed by examination of a simple blood smear.

A 45-year-old man was referred to our hospital in 2003 with a 3-week history of fever, cough, shortness of breath and fatigue, a 3-month history of diarrhea (3–4 times a day), and a 5-kg weight loss. The patient had been diagnosed with HIV 5 years previously but had refused treatment. Originally from Colombia, he had resided in Switzerland since 1979. Three months before hospital admission, he had visited his native country.

At the time of hospitalization, the patient was tachycardic and tachypneic, with a temperature of 39.6°C. Bilateral pulmonary rales and hepatosplenomegaly were noted. The abnormal laboratory findings were as follows: hemoglobin 7.9 g/dl, leukocyte count 9.9 G/l with left deviation of 36% and lymphopenia 6% (0.6 G/l), platelet count 17 G/l, C-reactive protein level 221 mg/l, alanine aminotransferase 152 U/l, aspartate aminotransferase 301 U/l, and serum creatinine 1065 µmol/l. The CD4+ cell count was 16/mm^3 and HIV RNA level 690,000 copies/ml. Chest radiograph showed diffuse, nodular, interstitial infiltrates. Five days after admission the patient developed bilateral pleural effusions. Due to gastritis, a gastroscopy was performed, revealing two pyloric ulcers.

The diagnosis of histoplasmosis was established by routine direct examination of a blood smear (Fig. 1a) and blood staining with calcofluor. Fungi were also seen in bronchoalveolar lavage (Fig. 1b), pleural liquid and bone marrow, and cultures of these samples grew *H. capsulatum*. Antimicrobial treatment was started with intravenous liposomal amphotericin B (250 mg/d for 13 days) and then switched to oral itraconazole (200 mg/d). Due to the patient's renal impairment, hemofiltration was necessary during the first 3 days, and his anemia was treated with transfusions of red blood cells. The patient also had several comorbid conditions, including cytomegalovirus chorioretinitis, Kaposi's sarcoma, oropharyngeal candidiasis and giardiasis, for which he received targeted treatment. His clinical evolution was slowly favorable, and he was transferred to a rehabilitation facility after 40 days.

At the time of transfer, the patient's levels of serum creatinine, transaminases and platelets had returned to normal, and his anemia had improved. Treatment consisted of itraconazole, valganciclovir, 3TC, tenofovir and cotrimoxazole. At 12-month follow-up, the patient's CD4+ cell count had risen to 145/mm^3, and no relapse had occurred. The decision was made to continue treating the patient with itraconazole until his CD4+ cell count reached 200/mm^3, at which time treatment would be switched to highly active antiretroviral treatment.

Although *H. capsulatum* has a worldwide distribution, it is more prevalent in certain parts of North America, Central and South America, Africa, and Asia [1]. Once regarded as a rare disease, it is now the most common endemic mycosis in the USA and one of the most common opportunistic fungal infections in HIV-infected patients living in areas of high prevalence [2], where it occurs in about 5% of AIDS patients [3].

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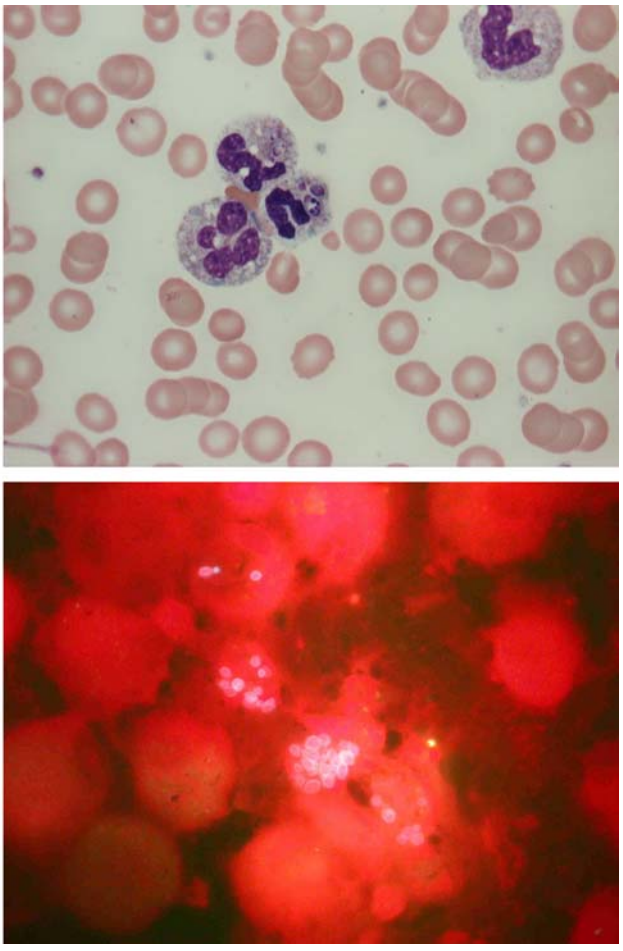

Fig. 1 **a** Wright-Giemsa stain of peripheral blood smear. Numerous circular inclusions with basophilic nuclei are visible in the cytoplasm of neutrophils. A surrounding clear capsule is also visible. In addition, the neutrophils have large granules and vacuoles indicating a severe infection. Elongated pale-blue Döhle bodies representing active rough endoplasmic reticulum can also be seen in the neutrophils on the left and at the bottom (enlargement 1000×). **b** Bronchoalveolar lavage stain viewed with calcofluor under a fluorescence-microscope

Among cases of histoplasmosis occurring in Europe, 69 cases due to *H. capsulatum* and 17 cases due to *H. dubosii* have been reported in the literature from 1980 to 1993, one-third of which occurred in AIDS patients [1]. The first case of disseminated histoplasmosis in Switzerland was diagnosed in 1984 in an HIV-infected patient from Zaire [4]. In the subsequent Swiss HIV cohort study, histoplasmosis accounted for 0.07% (11 cases) of all AIDS-defining diseases identified between 1987 and 2002. All of these patients had resided in endemic areas.

In nearly all reports of histoplasmosis in patients with AIDS, the infection has been disseminated [3, 5], while in the general population only 1 in 2,000 individuals develops disseminated infection [6]. An acute, rapidly fatal course with diffuse reticuloendothelial involvement characterizes the infection in these patients, and severity varies with the degree of immune deficiency [1]. Patients often present with shock, respiratory distress, hepatic and renal failure, obtundation, and coagulopathy [5]. Respiratory complaints, hepatosplenomegaly or lymphadenopathy are present in one- to two-thirds of cases. Skin or mucosal lesions are less frequent [5]. Although involvement of the gastrointestinal tract is common, gastrointestinal manifestations are relatively rare [7]. However, in certain cases gastrointestinal and/or hepatic signs and symptoms may predominate, and these patients may have no pulmonary symptoms [8]. Symptoms of gastrointestinal histoplasmosis can mimic other AIDS-associated pathologies, making the diagnosis difficult. In some cases, kidney lesions result from disseminated histoplasmosis, as shown by renal biopsy [9]. Skin involvement was found to be more common in a Brazilian than in a U.S. cohort [10]. Disseminated histoplasmosis with a neurological focus could present with symptoms mimicking cancer [11].

Recent guidelines for the treatment of disseminated histoplasmosis in patients with AIDS recommend a 12-week induction therapy, initially starting with intravenous amphotericin B deoxycholate, which can later be switched to itraconazole to complete the 12-week course [12]. Further investigation into the pathogenesis of disseminated histoplasmosis at the molecular level is necessary in order to identify new targets for the development of effective therapy to eradicate the infection in immunocompromised patients. For patients with AIDS, long-term maintenance therapy with itraconazole is required after a severe manifestation of histoplasmosis to prevent relapses. Coadministration with lopinavir/ritonavir led to a strong increase in itraconazole concentrations and its dosage must be adapted when used in this combination.

Early diagnosis is crucial for the positive outcome of disseminated histoplasmosis infection. Without treatment the mortality rate is 80%; however, with early diagnosis and antifungal therapy the mortality rate is usually <25% [11]. Therefore, it is important to recognize cutaneous histoplasmosis lesions so that prompt histologic evaluation and culture can be performed in suspected cases of disseminated fungal infection, thereby expediting diagnosis and treatment. Although immunocompromised patients may have a large number of organisms in a lesion with a minimal tissue reaction [8], serologic antigen tests for antibodies to *H. capsulatum* are positive in about 80% of patients with disseminated histoplasmosis [2].

In conclusion, histoplasmosis is a rare opportunistic infection in Europe, but it must be included in the differential diagnosis of opportunistic infections in HIV-infected patients, mainly if they are returning from endemic areas. Vigilance concerning the travel history of patients must be maintained. Fungal staining of blood and tissue samples, and even routine blood smear staining, point toward the diagnosis of this infection, which can be confirmed by the isolation of *H. capsulatum* in culture.

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