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Case Report

Complete blood count alterations in disseminated histoplasmosis



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Introduction

Classical histoplasmosis is a cosmopolitan fungal infection caused by *Histoplasma capsulatum* variety *capsulatum*.¹ *H. capsulatum* is a dimorphic fungus found in nature in its filamentous form, consisting of branched hyphae, which produce tuberculate macroconidia, the infective form of the fungus. When cultivated at 37 °C and in the tissues of infected people, it presents as budding yeast cells.¹

Histoplasmosis is a systemic mycosis that may affect previously healthy individuals. This disease may also be a disseminated opportunistic mycosis in patients receiving immunosuppressive drugs, those with hematologic malignancies, and in acquired immunodeficiency syndrome (AIDS) patients.¹

In immunocompromised patients, disseminated histoplasmosis usually affects the lymphatic tissues, liver, spleen, kidneys, meninges, and heart. *H. capsulatum*

has been found in its intracellular form in peripheral blood smears, in the bone marrow, and in lymph node aspirates.²

The clinical signs of disseminated disease include fever, night sweats, fatigue, weight loss, nausea, vomiting, and dyspnea.³ Cutaneous and mucosal lesions may also be detected. Severe cases may manifest as sepsis, with multiple organ dysfunction (including respiratory, hepatic, and renal failure) or concomitant meningitis. Mortality may reach 100% in AIDS patients without specific treatment.⁴

Laboratory abnormalities may also be present; pancytopenia due to bone marrow involvement is highly prevalent. Elevated transaminase, lactate dehydrogenase (LDH), and ferritin are common findings.⁵

The definite diagnosis is established with the isolation of *H. capsulatum* in culture or by direct detection of fungi in clinical samples. Cultures of respiratory samples, blood, and other materials, such as bone marrow, are still considered the gold standard for diagnosis. However, these cultures may take four to six weeks to grow and their sensitivity depends on the disease load.⁵

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Case report

A 47-year-old female patient, resident of Porto Alegre, RS, Brazil, presented to the emergency department of a tertiary hospital with complaints of dysuria, vomiting, right lower back pain, and altered level of consciousness over one week.

A family member reported that the patient had abdominal pain, urinary disorders, fever, and loss of appetite. The patient had been in the emergency department the previous week and was treated with antibiotics (nitrofurantoin) for urinary tract infection.

Her general condition was fair, and although she had difficulty to speak, she was able to answer questions and follow instructions. She was dehydrated.

Her vital signs were: blood pressure: 122/97 mmHg; axillary temperature: 35 °C; heart rate: 90 beats per minute; respiratory rate: 24 breaths per minute; and oxygen saturation: 92%. Physical examination showed a soft and painless abdomen; lung auscultation revealed some bilateral lung crackles, and heart auscultation was normal.

Laboratory tests showed the following result: urea level increased between first and second medical visit (seven days later) from 42 to 160 mg/dL and creatinine level increased from 0.97 to 5.01 mg/dL. Urine culture showed *Proteus mirabilis* resistant to nitrofurantoin. Treatment with cephalothin was initiated.

The initial diagnosis was acute pyelonephritis and acute renal failure due to the infectious process and dehydration. The patient was admitted to hospital.

On the 2nd day of hospitalization, there was clinical worsening, including blood dyscrasia. The patient was placed on mechanical ventilation, and the use of vasopressor for septic shock was initiated. She was transferred to the intensive care unit (ICU) and the antibiotic was replaced with piperacillin-tazobactam. An anti-HIV test was requested to rule out suspected HIV infection because previous tests showed leukopenia with lymphopenia and anemia. Dialysis was started.

Urea levels increased to 194 mg/dL, while creatinine levels increased to 6.28 mg/dL. A complete blood count did not show any significant changes: hemoglobin (Hb) 10.7 g/dL; hematocrit (Ht) 30%; total leukocytes $4.2 \times 10^9/L$; bands 9%; neutrophils 36%; lymphocytes 48%; monocytes 7%; however, erythroblasts ($1.05 \times 10^9/L$) were already detected.

On the 3rd day of hospitalization, the patient developed multiple organ dysfunction, including coagulopathy, and renal, circulatory, and pulmonary failure. On this day, she had petechiae on her chest and abdomen, as well as diffuse bleeding in the oral cavity, with lesions in the oral mucosa.

A complete blood count showed severe anemia: Hb 6.5 g/dL and Ht 18.6%. The patient received two units of packed red blood cells. There were no significant changes in the white blood count, but structures were found that could be bacteria or fungi. The microbiology department informed that the result of blood culture was negative for bacteria up to that moment, but there were changes, suggesting the presence of yeasts.

On the 4th day of hospitalization, the patient had anuria, cyanotic extremities, and refractory shock. The complete

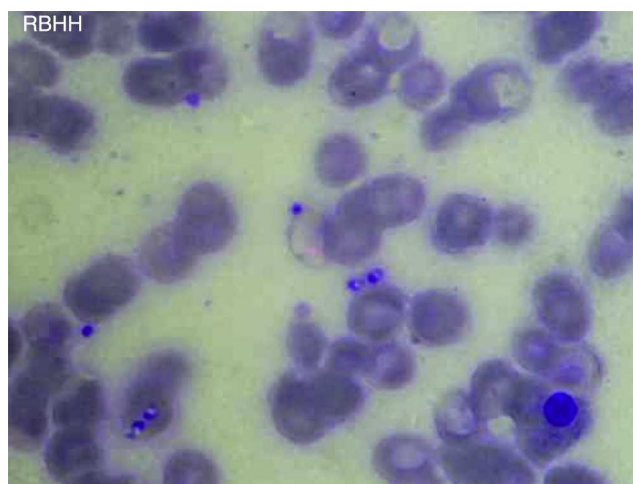


Figure 1 – Peripheral blood smear with several yeast cells of *Histoplasma capsulatum*.

blood count was significantly abnormal: Hb 6.9 g/dL; Ht 20%; erythroblasts $8.62 \times 10^9/L$; total leukocytes $0.5 \times 10^9/L$; neutrophils 10%; lymphocytes 80%; monocytes 10% and platelets $15.0 \times 10^9/L$.

There were a large number of platelet-like structures, with sizes that ranged from 2 to 4 μm that were suspected to be yeasts (Figure 1). Other structures were phagocytized by monocytes (Figure 2). After analysis of the findings by the microbiology department, the presence of yeasts was confirmed. In addition, some budding yeast cells were also detected after Gram staining of the blood culture sample.

Based on the laboratory information about the growth of yeasts in the blood culture, micafungin was initiated by the ICU medical team. Despite these measures, the patient died on that day.

The blood culture sample was further cultivated and the presence of *H. capsulatum* was confirmed. The anti-HIV test result was positive.

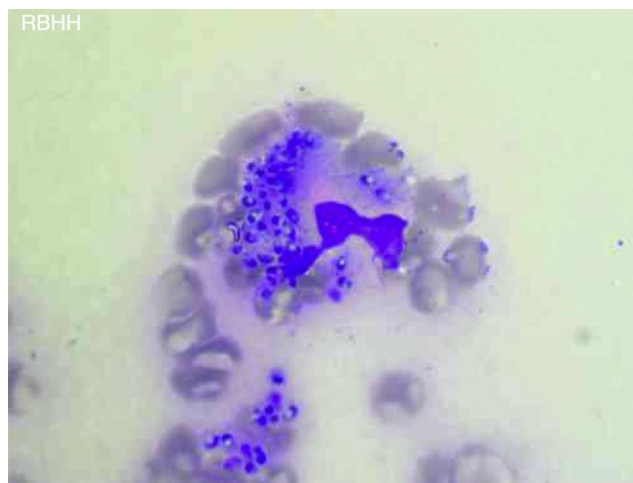


Figure 2 – Peripheral blood smear with several yeast cells of *Histoplasma capsulatum* and one monocyte.

Discussion

H. capsulatum consists of small (2–5 μm) oval structures, showing an evident clear halo around a central or eccentric stained chromatin. Therefore, it may be confused with *Candida glabrata*, *Penicillium marneffei*, *Pneumocystis (carinii) jiroveci*, *Toxoplasma gondii*, *Leishmania donovani*, platelets (measuring 1–4 μm in intracellular diameter) or staining artifacts.^{6,7} When these structures are detected in blood, they should raise a suspicion of disseminated infection, thus leading to an investigation.

Whenever the staff of a hematology department finds yeast-like organisms on a peripheral blood smear, the microbiology department should be informed and tests should be performed to identify the organisms.²

In the current case, the initial diagnosis was urinary infection. Suspicion of fungus infection was based on the analysis of the blood test slide. The definitive diagnosis was only established by blood culture, which is a time-consuming diagnostic test. Staining of a blood test slide is a simple and rapid diagnostic method. Its sensitivity depends on the disease load and it may be used in resource-limited settings.⁷

Disseminated histoplasmosis is often detected in AIDS patients. Unfortunately, in many individuals, HIV infection is only diagnosed when there are signs of opportunistic diseases.²

Early diagnosis of infection may be achieved by detecting the presence of yeast-like organisms in neutrophils or monocytes from peripheral blood. To confirm the diagnosis, fresh blood samples should be cultured. Other laboratory findings consistent with this condition are leukopenia, lymphopenia, and monocytopenia.²

Because of the potentially lethal characteristic of histoplasmosis, especially in AIDS patients, a definitive diagnosis should be established as quickly as possible.² As the culture can be a difficult and time-consuming process, other laboratory tests could be useful. Serum LDH levels higher than 1000 IU/L are found in patients with AIDS and disseminated histoplasmosis. Determination of serum ferritin is also useful in diagnosis, since values higher than 10 $\mu\text{g/mL}$ in patients with AIDS and disseminated histoplasmosis are highly specific markers of this condition.²

Therefore, a high degree of clinical suspicion, rapid and sensitive diagnostic methods, and appropriate specific treatment are necessary to reduce the mortality rate of AIDS patients with histoplasmosis.¹ The presence of persistent

fever and severe weight loss should raise the suspicion of HIV and opportunistic infections, such as tuberculosis and histoplasmosis.

Based on blood tests in southern Brazil, although disseminated histoplasmosis is common in patients with AIDS, its diagnosis is not often established. Yeast-like structures that are phagocytized by monocytes are found in advanced disease and there are few cases in our setting. Therefore, careful analysis of the slide is crucial in cases of suspicion of an infectious syndrome, even when a diagnosis of HIV-infection has not been established.

Unfortunately, in the present case, the detection of abnormal results in the blood test and blood cultures did not bring benefits to the patient because she died within a short period of time. There are cases in the literature showing that this suspicion helped to benefit patients because of early diagnosis and treatment.²

Conflicts of interest

The authors declare no conflicts of interest.

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