CASE REPORT

Diagnostic difficulties in disseminated histoplasmosis in an immunocompromised patient

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Abstract
An immunocompromised patient presented at the outpatient clinic with an oropharyngeal ulcer. Although disseminated histoplasmosis was considered, the diagnosis was rejected after negative serology of antibodies. Nevertheless, one month later, our patient was diagnosed with severe disseminated histoplasmosis, while admitted on the intensive care unit after intestinal perforation. Histoplasmosis is known for its late detection after primary infection. In most patients hematogenous dissemination occurs during acute infection before cellular immunity develops. Diagnosis is made through high index of suspicion at clinical presentation, thorough physical examination and a combination of an antigen immunoassay, serology of antibodies, cultures and histopathology. Histoplasmosis cannot be ruled out by any single test and should remain a clinical consideration in any at-risk immunocompromised patient with compatible symptoms.

Introduction
Immunosuppressant therapies compromise host defence, which may lead to secondary infections in immunocompromised patients. With suppressed T-lymphocyte function, a broad array of micro-organisms, both bacterial and viral or yeasts can cause disease in a patient. In immunocompetent patients, most infections with histoplasmosis are asymptomatic or self-limiting. However, immunocompromised patients can develop severe disseminated disease, many years after primary infection by histoplasmosis. This case report shows the fatal consequences of late diagnosis of disseminated histoplasmosis infection in an immunocompromised patient, after post-mortem kidney transplantation.

Case report
A 58-year-old Hindustani female patient was admitted postoperatively to the intensive care unit (ICU) after she underwent left-sided hemicolectomy because of perforation of the splenic flexure. Medical history included a post-mortem kidney transplantation due to renovascular disease two years before presentation, aortic and mitral valve replacement and successfully treated tuberculosis more than ten years previously. After her kidney transplantation, our patient was seen at regular intervals. Her immunosuppressant medication consisted of mycophenolate mofetil (1250 mg twice daily) and prednisone (10 mg daily).

Initially, prior to admission in our hospital, our patient was seen in the outpatient clinic of the dental surgeon with fever and an extremely painful ulcer in her mouth, for which she was treated with clindamycin. A few days later she was seen by her own nephrologist. The ulcer had not improved with the antibiotics and she was still febrile. A biopsy of the oral ulcer was performed, together with serological antibody tests for leishmaniasis and histoplasmosis. Suspicion of these possible diagnoses arose due to her Surinamese descent. The biopsy of the ulcer did not reveal a clear diagnosis, but showed a granulomatous infiltrate with an atypical mycosis, which was morphologically not compatible with Candida or histoplasmosis but was suggestive of pneumocystis. Pneumocystis was considered unlikely, since this comprises other clinical symptoms. The serological tests (direct agglutination) for leishmaniasis and histoplasmosis were negative and cultures did not show any micro-organisms or mycosis at that time. Initially the oral ulcer seemed to improve, but one month later, she developed subcutaneous skin lesions on her arms and legs for which she refused a biopsy. Six weeks after initial presentation, she was hospitalized because of progression of general discomfort and weakness, fever and a cough with a suspicion of interstitial pneumonia on chest X-ray.

Despite antibiotic treatment with cefuroxime our patient deteriorated on the second day of admission. She developed abdominal pains and a raised serum lactate, which was due to perforation of the colon at the lineal flexure; a hemicolectomy...
was performed and metronidazole was added. Clinical presentation on postoperative admission to the ICU showed multi-organ failure: she was sedated, ventilated and needed fluids, vasopressors and inotropics. On physical examination of our patient, as well as the post-operative findings, we saw the oral ulcer and an upper leg ulcer. No hepatomegaly or splenomegaly was present. Laboratory tests revealed severe bone marrow depression and a markedly elevated serum lactate dehydrogenase: 1262 U/l (ref < 248 U/l). Chest X-ray showed diffuse interstitial pulmonary infiltrates (see figure 1). Soon after admission continuous veno-venous hemofiltration was started.

Suspecting an opportunistic infection with a systemic mycosis or tuberculosis, a bone marrow biopsy and bronchoesoscopic alveolar lavage (BAL) was performed on ICU day two. Despite former negative test results, Grocott staining in both bone marrow and BAL indicated histoplasmosis (see figure 2), with yeasts as brownish oval elements into the cytoplasm of leukocytes. Subsequent histopathological examination of the colon and leg ulcer confirmed the diagnosis. Furthermore, all cultures of oral mucosa, leg ulcer, blood, ascites, bone marrow, sputum, bronchial lavage fluid, throat and tip of the central venous catheter returned positive for Histoplasma capsulatum (see figure 3), indicating severe disseminated disease. Liposomal Amphotericin B was added to the antibiotics. Despite optimal supportive care the patient deteriorated and died on the eighth day due to sepsis and multi-organ failure caused by disseminated histoplasmosis.

Discussion
Histoplasmosis is a systemic mycosis that is caused by the fungus Histoplasma capsulatum. It is most commonly seen in North and Central America. Most infections with histoplasmosis are asymptomatic or self-limiting. However, in the elderly, infants or immunocompromised patients, dissemination of the infection leads to severe illness with multiple organ involvement and is possibly lethal. Clinical manifestations of disseminated histoplasmosis are peripheral lymphadenopathy, hepatomegaly, splenomegaly, skin lesions, mucosal lesions or neurological symptoms. Possible laboratory findings include abnormal liver function tests, pancytopenia and elevated serum lactate dehydrogenase or ferritin values. Pulmonary dissemination may present with interstitial or reticulonodular infiltrates on chest X-ray. This case report describes several signs of dissemination of histoplasmosis on admission to the ICU: the patient suffered from unexplained colonic perforation, impaired bone marrow function and her chest X-ray showed interstitial infiltrates. Prior to admission, when seen in the outpatient clinic, the diagnosis of disseminated histoplasmosis seemed unlikely due to the negative serology (direct agglutination) for histoplasmosis antibodies. Also, histopathology of the

![Figure 1. Chest X-ray on ICU admission.](image1)

![Figure 2. Grocott staining indicative of histoplasmosis with yeasts as oval elements into the cytoplasm of leukocytes.](image2)

![Figure 3. Culture of histoplasmosis capsulatum yeasts.](image3)
oral ulcer did not show lesions compatible with typical histoplasmosis but was suggestive of pneumocystis. The pathologist recalled this conclusion when the cultures returned positive for histoplasmosis six weeks after the biopsy was taken: in retrospect, the same yeast forms were regarded as histoplasmosis.

As in our case, Antonello et al. has already showed that oral histoplasmosis in particular is closely associated with immunocompromised status and is the first presentation of disseminated histoplasmosis in the majority of cases described.5

The sensitivity of a Histoplasma antigen enzyme immunoassay (EIA) in urine is 73.3% in immunocompetent and 93.1% in immunocompromised patients.6 Serum Histoplasma EIA reaches a sensitivity of nearly 100%. Of all diagnostic tests, the highest sensitivity is achieved with both antigen enzyme immunoassay in serum or urine, with higher antigen levels in immunocompromised patients compared to the immunocompetent population.6

The sensitivity of anti-Histoplasma antibodies in serum is approximately 70% in immunocompromised and 90% in immunocompetent patients with disseminated disease. After solid organ transplantation, only a sensitivity of the antibodies test of 67% has been described in recent literature.7 It should be realized that in the acute phase of this disease, the serology of antibodies is often negative and should be repeated for they take up to one month to develop.

Unfortunately, neither repeated antigen enzyme immunoassay in urine or serum, nor serum antibodies was performed in our patient in the outpatient clinic. Receiving a negative result of one single test cannot rule out the diagnosis of disseminated histoplasmosis. Confirmation should be obtained by combining clinical suspicion and examination, Histoplasma EIA, antibodies level, light microscopy and microbiological cultures of the affected tissue.8

Although diagnosis was confirmed in our patient’s bone marrow, abdominal sepsis after perforation of ulcerative lesions in the colon also turned out to be caused by dissemination. Former research in patients with disseminated histoplasmosis showed that the gastro-intestinal tract is involved in 70-90% of autopsy studies.1 The associated lesions are diverse and differ from polypoid lesions and ulcerations to strictures and perforations, mainly seen in the colon.9,10

Liposomal Amphotericin B was initiated as soon as the diagnosis was confirmed; this is first choice treatment in hospitalized patients. Despite this, our patient deteriorated and died eight days after admission to the ICU. Johnson et al. found a clinical success rate of treatment in 88% of 81 patients with HIV and moderately severe to severe disseminated histoplasmosis. The rate of mortality was 2%.11 After clinical improvement, Amphotericin B can be switched to itraconazole as long-term therapy for at least a year. Chronic maintenance therapy should be considered in immunocompromised patients or relapse of disease after an episode of long-term treatment.12

In retrospect, our patient showed that although histoplasmosis was considered early on in the outpatient clinic, negative results led to incorrect reassurance and enabled the disease to be severely disseminated and complicated at time of admission. Furthermore, the patient’s refusal to undergo a skin biopsy also delayed the diagnosis.

If the diagnosis of disseminated histoplasmosis is suspected, it should not be rejected after negative serology of antibodies – especially not in immunocompromised patients, as false-negative test results may occur in up to 30% of cases. The diagnostic test for histoplasmosis with the highest sensitivity-specificity ratio is the antigen immunoassay.6 The combination of strong clinical suspicion, thorough physical examination, an antigen immuno assay, cultures and, if possible, histopathology of any found lesion should lead to the diagnosis.

References