Histoplasmosis is an infectious disease caused by the dimorphic fungus *Histoplasma capsulatum*. The endemic areas include the central and eastern states of the United States, South America, Africa and Asia. In nature, it exists as a mycelium in soil contaminated with excrement of birds and bats. When inhaled by humans or animals, it produces the yeast phase, which has an affinity for the macrophages that comprise the reticuloendothelial system.

Inhalation of *H. capsulatum* produces a lung infection with widely varying symptoms. In most people, it produces asymptomatic lung impairment that resolves without treatment. On the other hand, in some predisposed individuals it may cause chronic pulmonary disease or disseminated disease. Cases of disseminated and extrapulmonary histoplasmosis are uncommon. Nevertheless, they have been reported from endemic areas, particularly among immunocompromised individuals and in those at the age extremities. There is high incidence of liver, spleen, lymph node, bone marrow and adrenal involvement.

The clinical presentation of the disseminated disease includes pyrexia, anorexia, nausea, vomiting, weight loss and fatigue. These symptoms are nonspecific and resemble other chronic infections and malignancies.

**CASE REPORT**

A 74-year-old Caucasian male was admitted with a six-month history of daily fever, malaise, anorexia and weight loss of 7 kg. He lived in São Paulo, a large urban area, but used to go camping in rural areas, to go fishing. He had a 10-pack-year history of smoking and a 20-year history of alcohol abuse but had quit both habits over the past thirty years. He had been recently diagnosed with benign prostatic hyperplasia and was taking doxazosin. On physical examination, the patient appeared chronically ill, normotensive and feverish (axillary temperature of 39°C). Laboratory investigations showed normocytic anemia (hematocrit 28.1%, hemoglobin 9.4g/dl, mean corpuscular volume 82.6 fl); white blood cells 3,410/mm³ (neutrophils 60.7%, lymphocytes 23.4% and monocytes 13.1%); plasma glucose
110mg/dl; albumin 2.7g/dl; sodium 138 mEq/l; potassium 4.1mEq/l; and abnormal renal function with plasma urea of 57mg/dl and creatinine of 2.2mg/dl. Other blood tests were unremarkable and HIV serology was negative. Chest X-ray and urine microscopy were normal. Upper digestive tract endoscopy exposed slight antral gastritis. PSA, CEA and CA 19-9 assays were normal, as were the serum immunoglobulin levels. Several blood cultures were obtained, but they did not yield any bacterial or fungal growth.

**Radiological investigations were started.** Abdominal ultrasound revealed bilateral heterogeneous hypoechoic adrenal masses, measuring 5.4 x 5.0 x 4.5 cm on the right and 1.7 x 2.5 x 1.8 cm on the left side. Abdominal computed tomography (CT) showed, as the only finding, bilateral adrenal masses with central hypodense areas and minimal peripheral enhancement on contrast, and chest tomography revealed no abnormalities (Figures 1 and 2).

An ultrasound-guided fine-needle aspiration biopsy of the right adrenal gland yielded necrotic tissue with numerous organisms compatible with *Histoplasma capsulatum* (Figures 3 and 4). A diagnosis of disseminated histoplasmosis was made.

During hospitalization, the patient developed muscle weakness, arterial hypotension (blood pressure 90/60mmHg), diarrhea, hyponatremia (sodium 120mEq/l) and hyperkalemia (potassium 5.97mEq/l). A diagnosis of adrenal insufficiency was presumed (cortisol level of 6mcg/dl) and, because of the critical symptoms, treatment with hydrocortisone was started (100mg IV TID).

The patient was initially treated with amphotericin-B 1mg/kg/d, although on the second day of therapy the laboratory findings indicated renal function impairment (creatinine 3.6mg/dl). Therefore, therapy with itraconazole (400mg per day) was started. This led to an enormous improvement in the clinical condition and laboratory tests, and the patient was gradually weaned off corticosteroids.

The patient was discharged in an improved condition of health, taking itraconazole 400mg per day and prednisone 10mg per day. Seven months after discharge, the patient was readmitted because itraconazole treatment had been interrupted two weeks prior to this admission. He relapsed with fever and adrenal insufficiency, but rapidly responded to reintroduction of medication.

**DISCUSSION**

This case of an elderly male complaining of weight loss, daily fever, malaise and fatigue at first suggested malignancy. The presence of anemia reinforced this hypothesis. Because abdominal ultrasound revealed bilateral adrenal enlargement, the differential
diagnosis included benign or malignant adrenal tumors, metastatic tumors, subacute adrenal hemorrhage and disseminated infections such as histoplasmosis, paracoccidioidomycosis, tuberculosis, cryptococcosis and coccidioidomycosis. In a Brazilian series of 131,466 post-mortem examinations, there were 254 cases of adrenalitis, of which 43.7% were caused by tuberculosis, 33.8% by paracoccidioidomycosis and 1.2% by histoplasmosis.

The CT features of adrenal histoplasmosis include bilateral symmetric enlargement with preservation of normal outlines, peripheral enhancement and central hypodense areas. Other infectious causes such as paracoccidioidomycosis are indistinguishable from histoplasmosis on imaging, and metastasis may mimic infection because central necrosis is common in both conditions. Percutaneous biopsy or fine-needle aspiration using either CT or ultrasound guidance is necessary for evaluating adrenal lesions. Histopathological examination shows that the intracellular forms are situated within the cytoplasm of histiocytes, where they appear as numerous small spherical or oval yeast forms surrounded by a clear ring of space that resembles a capsule, hence the misnomer, *H. Capsulatum*. Despite its insensitivity, histopathology was essential for the definitive diagnosis of the present case. Additional diagnostic tests for diagnosing histoplasmosis, such as tissue sample culturing, antigen detection, serology and molecular diagnosis by polymerase chain reaction were not available at that time.

Disseminated histoplasmosis may affect almost all systems, including the reticuloendothelial system, lungs, gastrointestinal tract, renal tract, central nervous system, bone marrow and adrenal glands. It usually occurs in immunocompromised individuals or at age extremes. Histoplasmosis presenting as bilateral adrenal enlargement has been previously described. However, to our knowledge, this is the fourth report of bilateral adrenal histoplasmosis associated with adrenal insufficiency in an immunocompetent host. Twelve cases of bilateral adrenal histoplasmosis have been reported in immunocompetent hosts and only three of them presented with adrenal insufficiency. Despite his age, this patient had no evidence of immunosuppression and the discrete lymphocytopenia on admission could have been caused by the infection itself.

Treatment with corticosteroids was promptly started without first having a complete laboratory diagnosis of adrenal insufficiency, which would have been obtained from the blood cortisol level and the low ACTH stimulated cortisol responses. Among patients with adrenal insufficiency, a large proportion require replacement therapy, although reversal of adrenal dysfunction has been described after prolonged antifungal treatment.

The recommended treatment is amphotericin B for critically ill hospitalized patients. Nevertheless, this had to be replaced by itraconazole because of nephrotoxicity. Itraconazole is well tolerated and has excellent central nervous system penetration. Ketoconazole may be used in milder presentations. Recurrence has been described as long as nine years after cessation of treatment, and therefore treatment duration of one to two years reduces the risk of relapse. This case emphasizes the fact that adrenal histoplasmosis does occur in immunocompetent patients and has to be considered in the differential diagnosis of bilateral adrenal masses. Adrenal insufficiency has to be monitored and antifungal therapy should be maintained for at least one year.

**References**


