

CASE REPORT

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Fatal Disseminated *Cryptococcus* as the Initial Presentation of HIV Infection in the Era of Highly Active Antiretroviral Therapy

ABSTRACT: Despite the availability of highly active antiretroviral treatment, many HIV-positive patients still present for the first time with a low CD4 count or an acquired immune deficiency syndrome (AIDS) defining illness. This may be due to patients' refusal to be tested for HIV, delay in seeking medical treatment, or the misdiagnosis of an AIDS-associated condition. We present a 39-year-old African American male with undiagnosed HIV, who died shortly after arrival to the emergency room. An autopsy was performed at the Dallas County Medical Examiners' Office, and the cause of death was determined to be disseminated cryptococcosis. Further investigation at autopsy revealed HIV 1/2 antibody positivity and HIV western blot positivity. This case demonstrates the importance of considering complications of HIV as a cause of death, even when the patient has no prior history.

KEYWORDS: forensic science, HIV, autopsy, *Cryptococcus*

Case Report

A 39-year-old African American male presented to the emergency room complaining of weakness, malaise, headache, vomiting, and skin lesions for at least 1 week. The patient's only positive past medical history was for two episodes of Staphylococcal osteomyelitis, with the most recent episode 3 years prior, and he was taking no medications at the time of presentation.

Physical examination upon arrival to the emergency room showed the patient to be well-nourished, awake, alert, oriented, and in mild distress, with diaphoresis and shortness of breath. The patient also had numerous dome shaped papules with crusting and umbilication on the face, oral mucosa, and extremities. Further testing showed the patient to be afebrile, hypoxic (O₂ saturation = 89%), tachycardic (118 beats/min), and hypotensive (blood pressure = 78/40). The Patient also had respiratory alkalosis and metabolic acidosis (CO₂ = 15 mEq/L) and hyponatremia (125 mEq/L). The patient was started on IV fluids, antibiotics, and dopamine. Before the patient could be transferred to the ICU, he vomited, became unresponsive, developed agonal breaths, and was intubated. The patient arrested and was pronounced dead after unsuccessful attempts at resuscitation.

External examination of the patient at autopsy showed a relatively well-developed 39-year-old African American male with numerous dome shaped papules, which ranged in size from 0.5 to 1.0 cm in diameter. The papules were distributed on the oral mucosa, face, and extremities, and many demonstrated central crusting and/or umbilication (Fig. 1).

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The internal examination was remarkable for a grainy appearance to the leptomeninges, pulmonary edema, a 1 cm nodular mass in the upper lobe of the left lung, numerous 0.1–0.2 cm nodules within the cortex and medulla of the kidney (Fig. 2), a markedly enlarged spleen, and markedly enlarged parabrachial lymph nodes. Examination of the brain after formalin fixation showed slight sulcal prominence in the frontal and temporal regions, as well as mild to moderate narrowing of the lateral ventricles.

Microscopic examination showed budding yeast, consistent with *Cryptococcus*, within the lungs, skin (Fig. 3), adrenal glands, liver, and kidneys (Fig. 4). Microscopic examination of the brain showed cryptococcal meningitis with diffuse extension along Virchow-Robin spaces into the cortex, basal ganglia, cerebellum, and mid-brain. Hypoxic and ischemic changes with cerebral and cerebellar swelling were also identified. Mucicarmin stains were used to highlight the yeast-like organisms and surrounding capsule.



FIG. 1—Papules on the oral mucosa and face with central crusting and umbilication.

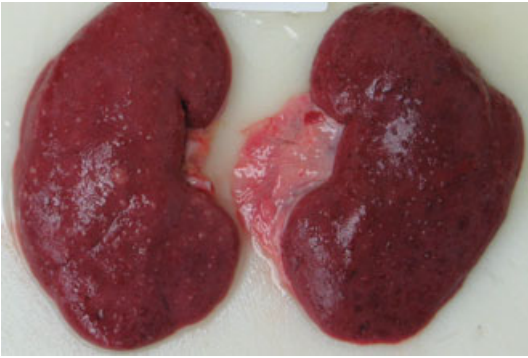


FIG. 2—Numerous small nodules within the cortex and medulla of the kidney.

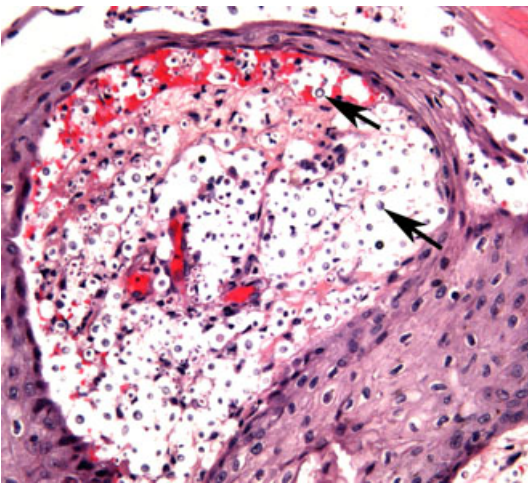


FIG. 3—Budding yeast, consistent with *Cryptococcus* (arrows), within the dermis (hematoxylin and eosin staining).

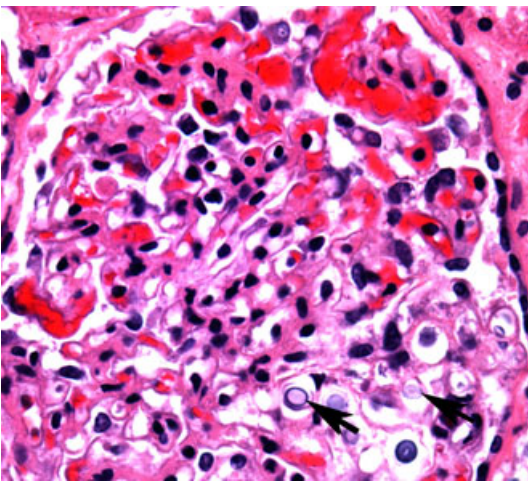


FIG. 4—Budding yeast, consistent with *Cryptococcus* (arrows), within the kidney (hematoxylin and eosin staining).

Further investigation at autopsy revealed positive blood cultures for *Cryptococcus neoformans*, HIV 1/2 antibody positivity, and HIV western blot positivity.

Discussion

The availability of highly active antiretroviral treatment (HAART) in the United States has led to a dramatic increase in the number of patients willing to undergo testing for HIV (1). The increase in testing, combined with the availability of treatment, has led to a significant decline in the number of patients with advanced disease. Even in the era of HAART, however, many HIV-positive patients still present for the first time with a CD4 count of less than 200 or an acquired immune deficiency syndrome (AIDS)-defining illness. In 2004, Girardi et al. (2) analyzed almost one thousand HIV-positive, antiretroviral-naïve patients who were presenting for HIV-related medical care for the first time during the HAART era. Over one-third of these patients had a CD4 count less than 200/mm³, and almost one-fifth had clinically defined AIDS. Another study by Sabin et al. (3) in 2006 reported that one-fifth of all HIV deaths, even in recent years, occurred in late presenters who were diagnosed with the infection within 6 months of death.

Not only do patients still present in the late stages of infection, but also some are initially diagnosed with HIV at autopsy after developing a fatal AIDS-defining illness. This may be due to patients' refusal to be tested for HIV, delay in seeking medical treatment for the ultimately fatal illness, or the misdiagnosis and subsequent mistreatment of the AIDS-defining illness. Our patient had not been previously tested for HIV, and he did not have a regular primary care physician. He also waited until the reported illness had advanced for at least 1 week before presenting to the emergency department.

A previous report by Bouffard et al. (4) highlights the misdiagnosis of an AIDS-defining illness and subsequent diagnosis of HIV occurring at autopsy. A 63-year-old African American man developed neurological symptoms, including clumsiness, gait instability, and masked facies, and was diagnosed clinically with early Parkinson's disease (PD). Other symptoms that were present during his initial diagnosis of PD included a persistent cough and a substantial weight loss over several months; however, further work-up was negative and no HIV testing was performed. The patient died 8 months after his initial neurologic symptoms. Autopsy examination showed numerous microabscesses with cryptococcal organisms in the substantia nigra, caudal thalamic region, lungs, and kidneys. Blood at autopsy was positive for HIV, and the cause of death at autopsy was disseminated cryptococcal infection due to HIV infection.

In both cases, the microscopic diagnosis of an AIDS-defining illness led to the initial diagnosis of HIV at autopsy. Our patient presented with numerous dome shaped papules with umbilication and crusting, and the clinical differential diagnosis of these lesions included widespread molluscum contagiosum or disseminated cryptococcosis, both of which led to suspicion of HIV infection. A skin biopsy provided the diagnosis of cutaneous *Cryptococcus*, and the observation of cryptococcal organisms in numerous other organs led to the diagnosis of disseminated cryptococcosis. Positive testing for HIV infection was then confirmed.

Disseminated cryptococcosis is a systemic fungal infection, caused by *Cryptococcus neoformans*, which often develops in the setting of severe immunosuppression. Cryptococcosis is a leading cause of the morbidity and mortality attributable to fungal infections in patients with AIDS (5). Patients with HIV/AIDS, and CD4 counts less than 100 cells/mL, are at particular risk for this infection, and the disseminated disease most likely develops through hematogenous spread after inhalation of the organisms into the lungs.

The most common clinical manifestations of disseminated cryptococcosis include headache, fever, and nuchal rigidity, which are signs related to the development of cryptococcal meningitis (6). After the central nervous system, the most likely sites of involvement are the lungs and skin. Other body sites that may be affected include the eyes, kidneys, prostate, adrenals, heart, liver, spleen, bone, muscle, lymph nodes, and thyroid (5).

A presumptive diagnosis of disseminated cryptococcosis can be made by the detection of the cryptococcal polysaccharide capsular antigen in the cerebrospinal fluid and other body fluids, including serum and urine, by latex agglutination (5). Definitive diagnosis is made through culture of affected fluid or tissue, with demonstration of the encapsulated, round to oval, yeast that typically measures 4–6 μm in diameter. Tissue may also be examined histologically, and the cryptococcal organisms may be seen on routine histology or using special stains, such as mucicarmine or periodic acid–Schiff (PAS).

In summary, within this era of HAART, few cases of HIV infection are diagnosed at the time of autopsy in association with fatal AIDS-defining illnesses. The above cases demonstrate the importance of considering complications of HIV as a cause of death, even when the patient has no prior history.

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