

## CASE REPORT

### DISSEMINATED HISTOPLASMOSIS IN A RENAL TRANSPLANT CHILD

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**Abstract.** Disseminated histoplasmosis has occasionally been documented in solid organ transplant patients in some endemic areas. Early diagnosis and treatment are associated with good outcomes. In this report the authors describe the clinical characteristics and natural history of undiagnosed disseminated histoplasmosis in a child who underwent a cadaveric renal transplant at a tertiary healthcare center in northeastern Thailand.

**Keywords:** histoplasmosis, renal transplant, disseminated, child

#### INTRODUCTION

Histoplasmosis is an endemic mycosis in Central and South America, some areas of Africa and in South East Asia. The severity of histoplasmosis depends upon host immunity and quantity of inoculum exposure. Most infections are asymptomatic and/or self-limited but severe disseminated disease does occur in immunocompromised patients, including solid organ transplant recipients (Hood *et al*, 1965; Brett *et al*, 1988; Limaye *et al*, 2000; Sethi, 2005; Freifeld *et al*, 2005; McGuinn *et al*, 2005; Tan *et al*, 2005; Dwyre *et al*, 2006; Oh *et al*, 2006; Einollahi *et al*, 2008; Koo *et al*, 2008; Marques *et al*, 2008; Cuellar-Rodriguez *et al*, 2009; Pourfarziani and Taheri *et al*, 2009; Rekha *et al*, 2010). We report here the clinical manifestations

of disseminated histoplasmosis, which caused the death of a renal transplant child at Srinagarind Hospital, a tertiary care university hospital in northeastern Thailand.

#### CASE REPORT

A 15-year-old girl with a history of end-stage renal disease secondary to focal segmental glomerulosclerosis underwent a cadaveric renal transplant in August, 2007. Her immunosuppressant regimen on presentation was comprised of tacrolimus, mycophenolate mofetil (MMF) and prednisolone. A serum creatinine level one month prior to admission was 1.4 mg/dl.

Eleven months after renal transplantation, the patient developed intermittent high-grade fever and chills without other symptoms lasting one week. The physical examination was unremarkable except for high-grade fever.

Initial laboratory findings were:

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hemoglobin, 11.8 g/dl; white blood cell count,  $4.1 \times 10^9/l$ ; platelet count,  $247 \times 10^9/l$ ; serum creatinine, 1.4 mg/dl; cholesterol, 173 mg/dl; albumin, 3.3 g/dl; globulin 2.9 g/dl; total bilirubin, 0.4 mg/dl; direct bilirubin, 0.1 mg/dl; alanine aminotransferase, 48 U/l; aspartate aminotransferase, 42 U/l; alkaline phosphatase, 285 U/l; and tacrolimus trough level, 6.4 ng/ml. More than 100 white blood cells per high power field were noted in her urine. The chest x-ray and abdominal ultrasound examinations were unremarkable.

Intravenous ceftriaxone was administered and the mycophenolate mofetil was discontinued. The blood culture was negative and a cytomegalovirus viral load was  $< 600$  copies/ml. A urine culture was not obtained.

After a 10-day course of ceftriaxone, the patient continued to have fever without other symptoms. The repeated urine analysis showed 0-1 white blood cell per high power field so the ceftriaxone was discontinued. Multiple complete blood counts were normal except for a gradual reduction in hemoglobin level.

Investigations were negative for leptospirosis, scrub typhus, murine typhus, melioidosis and hepatitis B and C. The transplanted kidney biopsy showed mild interstitial fibrosis and tubular atrophy.

Two weeks after discontinuation of ceftriaxone, the patient experienced cough and fever. Repeated chest x-ray demonstrated mild interstitial infiltration of both lungs, which was treated with roxithromycin. The patient's symptoms then worsened: she developed dyspnea, leg myalgia, watery diarrhea and hypoxemia. Neither pus cells nor enteropathogens were seen in her stools. Intravenous imipenem, high-dose cotrimoxazole and ganciclovir were administered empirically.

The patient then developed disseminated intravascular coagulopathy. Packed red blood cells, cryoprecipitate and platelet concentrate were given, without improvement; the patient then developed respiratory distress syndrome. An endotracheal tube was inserted and the patient was placed on ventilator support. A bilateral miliary pattern of pulmonary infiltrates and pleural effusion were found on repeated chest x-ray; vancomycin was then added intravenously.

The patient developed oliguria and the serum creatinine rose to 3.2-3.8 mg/dl. Acute hemodialysis was initiated and the dosage of tacrolimus was decreased. Repeated blood and urine culture were negative for bacteria and fungus but *Candida albicans* was isolated from a tracheal suction culture. Amphotericin B was administered intravenously but her symptoms did not improve. The patient required greater pressure with the ventilator and subsequently developed a right pneumothorax which was treated with a chest tube. The patient developed cardiac arrest and expired due to severe pneumonia.

At autopsy mononuclear phagocytes filled with numerous small intravascular yeast consistent with *Histoplasma capsulatum* were found in the lung and liver (Figs 1 and 2) but were absent in the transplant kidney tissue.

## DISCUSSION

The number of children receiving solid organ transplants in Thailand has increased over the last decade because of (a) financial support from the government and (b) an increase in organ donations. Infection is a significant problem among this group of patients (Wisanyotin and Jiravuttipong, 2009). Invasive fungal in-

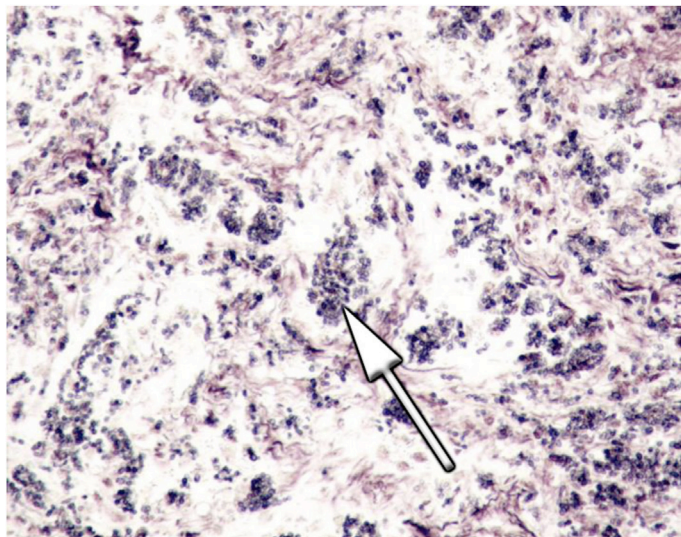


Fig 1—Clusters of *H. capsulatum* yeast in lung tissue (Gomori methenamine silver staining).

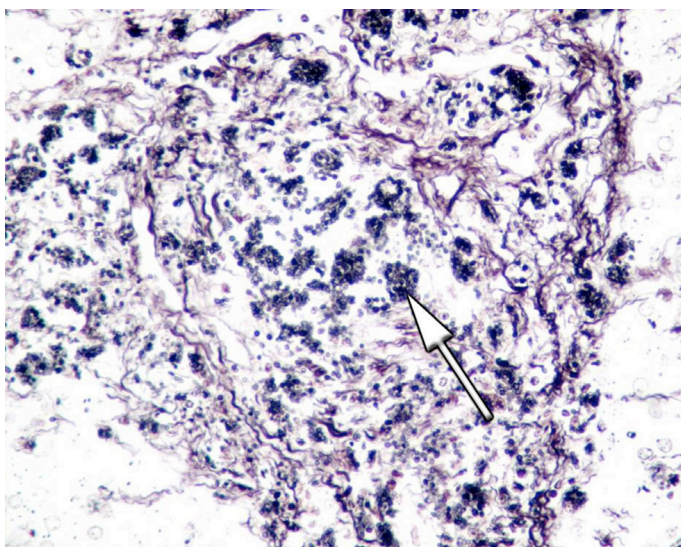


Fig 2—Clusters of *H. capsulatum* yeast in liver tissue (Gomori methenamine silver staining).

fections (IFIs) were reported in 21 of 2,410 renal transplant recipients (0.87%) from Iran (Einollahi *et al*, 2008). The majority of IFIs in that report were mucormycosis, with the least number of cases being his-

toplasmosis. *Histoplasma capsulatum* infection is uncommon in Thailand. It has been found mostly in northern Thailand, especially among patients infected with human immunodeficiency virus. The incidence of post-transplantation histoplasmosis in Thailand is unknown. In an endemic area of Cleveland, Ohio (Cuellar-Rodriguez *et al*, 2009), USA, the incidence of histoplasmosis among solid organ transplant recipients was 1 case per 1,000 person-years and the incidence was 0.11-1.9% in Nebraska, USA (Freifelf *et al*, 2005).

There are three modes of infection with histoplasmosis: (a) inhalation of soil contaminated with bird or bat excreta, (b) endogenous reactivation and (c) transmission from donor-infected tissue. The patient in the present study was likely infected from either a contaminated environment or endogenous reactivation since no organism were found in the transplanted kidney tissue. There was no history of exposure to birds or bats from retrospective interview with the patient's parents.

A diversity of clinical manifestations in patients infected with disseminated histoplasmosis has been reported: prolonged fever, subacute respiratory symptoms, diarrhea, diaphoresis, headache and acute renal failure (Brett *et al*, 1988; Limaye *et al*, 2000;

Sethi *et al*, 2005; Dwyre *et al*, 2006; Oh *et al*, 2006; Marques *et al*, 2008; Pourfarziani and Taheri *et al*, 2009; Rekha *et al*, 2010). Atypical presentations include: cellulitis (McGuinn *et al*, 2005), a soft-tissue chest wall mass (Koo *et al*, 2008), pulmonary nodules (Tan *et al*, 2005) and diffuse thrombocytopenic purpura (Hood *et al*, 1965).

Histoplasmosis is usually diagnosed from fungal stains, culture of affected tissue, antigen detection or a serologic test. Serum or urine antigen detection by enzyme immunoassay is the most rapid and sensitive diagnostic test for disseminated histoplasmosis. The sensitivity of antigen detection is as high as 90-95% (Connolly *et al*, 2007); however, neither this antigen test nor *Histoplasma* serology testing are available in Thailand. Culture of infected tissue is, however, a useful method for detecting histoplasmosis albeit less sensitive and needs longer duration to complete. In the present study, multiple blood, urine and tracheal suction cultures were negative for histoplasmosis despite her suffering from disseminated histoplasmosis. Histopathologic examination of infected tissue is another useful diagnostic method but our patient's severe hypoxemia and high mechanical ventilator settings made performing bronchoalveolar lavage and lung biopsy impracticable.

Histoplasmosis is uncommon in non-endemic areas and initial presentations are protean. A high index of suspicion is necessary for early recognition and timely performance of diagnostic investigations. A rapid diagnosis and appropriate treatment are essential to have a satisfactory outcome with disseminated histoplasmosis. Successful outcomes with treatment of disseminated histoplasmosis using amphotericin B followed by a prolonged

course of itraconazole or voriconazole have been documented (Frifeld *et al*, 2005; Cuellar-Rodriguez *et al*, 2009). When there is a scarcity of laboratory studies (*ie*, antigen detection, the most rapid and sensitive) for identifying disseminated *H. capsulatum*, an antifungal drug should be considered empirically in renal transplant patients presenting with a prolonged febrile illness when there is a lack of evidence for the presence of bacteria or virus infection.

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