Histoplasmosis in Renal Transplant Patients in an Endemic Area at a Reference Hospital in Medellin, Colombia

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ABSTRACT

Background. Histoplasmosis is an uncommon systemic fungal infection, but it is potentially fatal in immunosuppressed populations. In Latin America, which is considered an endemic area for this mycosis, there have been no published reports regarding the incidence, clinical presentation, morbidity, and mortality of histoplasmosis in renal transplant patients. The objective of this study was to describe cases of histoplasmosis in renal transplant patients treated at the Pablo Tobon Uribe Hospital (Medellin, Colombia) between 2006 and 2013.

Methods. This is a descriptive, retrospective study.

Results. The incidence of histoplasmosis in our renal transplant population was 1.1%. The ages of the 9 patients (4 men and 5 women) ranged between 27 and 59 years. In 2 of these patients, histoplasmosis appeared during the first year after transplantation. At the time of transplantation, 66% of patients received induction with alemtuzumab; 88% had a prior rejection episode and required increased immunosuppressive medication; 88% had renal graft dysfunction with creatinine levels >1.5 mg/dL; and the primary clinical presentation was disseminated histoplasmosis followed by the pulmonary form of the disease. Diagnoses were performed by histology in 6 patients, blood culture in 2 patients, and antigenuria in 1 patient. Three patients required treatment with amphotericin B for the severity of their infection, and 2 of these patients died before receiving the cumulative dose of amphotericin B. The 7 remaining patients received itraconazole for 12 months and had a successful treatment response. Regarding complications, 2 patients had hemophagocytic syndrome. At the 1-year follow-up appointment, renal function remained stable in all patients, and no patients had acute rejection or required renal replacement therapy. Thus, the overall mortality rate observed was 22.2%.

Conclusions. In this series, histoplasmosis in renal transplant patients presented as an aggressive opportunistic infection with a higher incidence than that previously reported in the literature. The following risk factors have been associated with histoplasmosis: renal graft dysfunction, previous acute rejection, immunosuppression with tacrolimus-mycophenolate, and induction with alemtuzumab. The clinical presentation of histoplasmosis was nonspecific, which complicated disease diagnosis, and the treatment regimens were highly toxic and associated with significant morbidity and mortality rates.

ALTHOUGH the existence of histoplasmosis has been suggested since antiquity, the modern history of this fungal infection began in 1906 with the findings of Samuel T. Darling after he performed an autopsy on a 27-year-old

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man who was working in the construction of the Panama Canal. The microorganism observed in the autopsy was described by Darling as "an egg- to round-shaped parasite, surrounded by a clear halo, with a thickness approximately 1/6th the diameter of the parasite." Because of its similarities with *Leishmania*, Darling thought that the microorganism was a protozoan and that the halo was a capsule. Consequently, he called the microorganism *Histoplasma capsulatum*. Despite the fact that the microorganism was not actually a protozoan and no such capsule was present, the name has lasted until today [1].

Histoplasmosis is an opportunistic fungal infection caused by the dimorphic fungus *H capsulatum*. The clinical spectrum of infection ranges from a self-limited febrile illness to severe multi-organ dysfunction, depending on the size of the inoculum in the host and the immune status of the affected individual [2]. Histoplasmosis occurs worldwide, but it is most common in temperate and tropical climates. Endemic areas with the highest number of known cases are located in the eastern half of the United States (particularly the Ohio-Mississippi river valley) and Latin America, where the disease has a significant impact on public health [3].

In transplant patients, the alterations in cellular immunity that occur secondary to the use of potent immunosuppressants have led to an increased risk of opportunistic infections, including systemic fungal infections [4–7]. These types of infections occur most frequently during the first year after transplantation [8,9]. Previous data from the Transplant Associated Infection Surveillance Network (TRANSNET), which includes 22 centers of solid and hematopoietic organ transplantation in the United States, reported an incidence of invasive fungal infection of 3.1% [10], 80% of which were caused by Candida and Aspergillus [9].

Histoplasmosis occurs in 0.1% to 0.5% of renal transplant patients [5,11], but its incidence varies according to the endemicity of each region. The most complete case series described in the histoplasmosis literature in solid organ transplants corresponds to cases in the endemic area in the United States [12–15]. Latin America is also an endemic area for histoplasmosis, which is the second most common human systemic mycosis in South America (after paracoccidioidomycosis). Histoplasmosis has been reported with the highest frequency in Argentina, Brazil, Venezuela, and Uruguay, and it has been found less frequently in northern Chile, Peru, Colombia, Guyana, Bolivia, and Paraguay [16].

Colombia is included in the endemic area, and the department of Antioquia has been described as an area with a large number of reported cases. Arango et al [17] reported the largest series of histoplasmosis in Colombia and Latin America observed to date, with 434 cases identified over a period of 16 years (1992 to 2008). In this series, a surprising number of patients (257 patients, 59.2 %) were residents in the department of Antioquia, and the transplant population was 13.8% [17].

Despite the large number of patients with histoplasmosis in this region, epidemiological and clinical data are scarce and diverse [4,18,19], and the prevention, diagnosis, and treatment of this disease remain difficult [20]. The increased recognition of the importance of histoplasmosis has led to the development of new diagnostic approaches and greater efforts to better understand the epidemiology and pathogenesis of this condition. Knowledge of local epidemiology is particularly important for clinicians to reach a diagnosis and to make appropriate treatment decisions.

The Pablo Tobon Uribe Hospital, which is located in Medellin, Antioquia (the department capital), is a transplant reference center where patients come from various parts of the department and the country. This study aims to provide clinical and laboratory descriptions of histoplasmosis and to discuss the treatment responses observed in renal transplant patients at the Pablo Tobon Uribe Hospital in Medellin, Colombia, between 2006 and 2013.

METHODS

This retrospective study was conducted at the Pablo Tobon Uribe Hospital in Medellin, Colombia. Renal transplant patients with histoplasmosis diagnoses, which were confirmed by histological findings, blood cultures, or antigenuria between 2006 and 2013, were included in the study. All data were obtained from medical records and recorded in an Excel database. Demographic, clinical, and laboratory data were included in the study, as were the associated risk factors for histoplasmosis, including a previous rejection, increased immunosuppressive medication, and having been administered drug treatment. In addition, several outcomes, such as death and graft survival, were evaluated.

The SPSS statistical software package (version 18) was used for statistical analysis. Descriptive statistics are presented for all data, including the absolute numbers and percentages for qualitative characteristics and the ranges for quantitative variables.

This study was approved by the ethics committee of the Pablo Tobon Uribe Hospital. The study was conducted in accordance with the ethical standards of research on humans included in Resolution 008430 of 1993, of the Ministry of Social Protection, Republic of Colombia. The researchers agreed to respect the confidentiality and privacy of information in the clinical records. This study did not consider interventions in the study population (ie, there were direct physical examinations, laboratory tests, or treatments), and thus it posed no risks to the participants.

RESULTS

Of the 613 kidney transplants that were performed at the Pablo Tobon Uribe Hospital between 2006 and 2013, 7 patients received a confirmed diagnosis of histoplasmosis. Two other patients were also diagnosed, but they had received transplants at another hospital in the city of Medellin. Some of the baseline characteristics of the patients are described in Table 1. All patients received kidney transplants from deceased donors. Four of the patients were men, and 5 were women. Six of the patients received induction therapy with alemtuzumab during the transplant (30 mg IV), and intravenous boluses of methylprednisolone were administered over several days (500 mg on day 1, 250 mg on day 2, and 125 mg on day 3). In 3 patients, induction therapy consisted of only 500 mg intravenous methylprednisolone for 3 days. Of the patients examined