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CASE REPORT

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Disseminated histoplasmosis in pediatric kidney transplant recipients—A report of six cases and review of the literature

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Abstract

Background: We report a case series of histoplasmosis in KTx patients in a children's hospital in an endemic area.

Methods: All KTx cases from January 1, 2002, to August 31, 2016, were reviewed to identify those with disseminated histoplasmosis.

Results: The attack rate of histoplasmosis among our KTx patients was 6.9 per 100 cases. The median age at the time of diagnosis was 16 years (11-18). Comorbidities included glomerulosclerosis (3), medullary cystic disease (1), and obstructive uropathy (2) and HIV (1). There were 5 deceased and 1 living-related donor transplants, and no patient had a history of rejection prior to histoplasmosis. Median time from transplant to histoplasmosis was 14.8 months (IQR 2.2-38.3) and 33% occurred in the first year after transplant. Urine and/or serum antigens were positive in all patients. They were either treated with amphotericin B and transitioned to an azole or received azole monotherapy. Most (83%) received chronic suppression with itraconazole. No patients died and relapse occurred in 1 patient after repeat transplant.

Conclusions: KTx patients in endemic areas are at risk for disseminated histoplasmosis. Further study is needed to determine which factors portend the need for fungal prophylaxis in this subset of patients.

KEYWORDS

kidney transplant, histoplasmosis, pediatrics, immunosuppression

1 | INTRODUCTION

Histoplasmosis is caused by the saprophytic dimorphic fungus *Histoplasma capsulatum*. The fungus is endemic to the Ohio and Mississippi River valleys of the United States as well as to regions of Central and South America, Africa, Australia, and Asia. In the endemic areas of the United States, infections are common but are asymptomatic in most cases. Progressive disseminated histoplasmosis, however, is an opportunistic infection occurring in individuals with congenital or acquired cellular immune dysfunction.[1] SOT recipients have T-cell immune dysfunction, resulting from immunosuppressive agents putting them at risk for disseminated histoplasmosis from de novo infection or recrudescence of a previously controlled infection.[2-6] They often become symptomatic during the period of dissemination due to their impaired ability to control the infection.

Published reports from adult transplant programs in endemic regions report the rate of disseminated histoplasmosis in SOT

Abbreviations: BAL, bronchoalveolar lavage; ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; GMS, Gomori Methenamine-Silver Nitrate stain; IDSA, Infectious Diseases Society of America; IQR, interquartile range; KTx, kidney transplant; MAC, *Mycobacterium avium* complex; SOT, solid organ transplant; VATER, vertebral anomalies, anal atresia/imperforate anus, tracheoesophageal fistula, renal anomalies.

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recipients at approximately 0.5%. A third to one-half of these cases occur within the first year following transplant.[7,8] There are limited data available on histoplasmosis in pediatric SOT recipients. Specific knowledge gaps include the risk of disease, clinical course and outcomes, and the role of antifungal prophylaxis. Children represent a unique population given their differences in immunity as well as pharmacokinetics of antifungals in comparison with adults. The objective of this case series was to review the clinical presentation, management, and outcomes of disseminated histoplasmosis cases in pediatric KTx recipients.

2 | PATIENTS AND MATERIALS

This study was approved by the Institutional Review Board of the University of Tennessee Health Sciences Center. We reviewed all children diagnosed with disseminated histoplasmosis following KTx presenting to Le Bonheur Children's Hospital in Memphis, TN, between January 2002 and August 2016. At the time of histoplasmosis diagnosis, the study population ranged in age from 11 to 18 years of age. Disseminated histoplasmosis infection was defined as clinical or laboratory evidence of multiorgan involvement in conjunction with positive serum and/or urine *Histoplasma* antigen tests. We collected clinical data including demographics, comorbid conditions, immunosuppressive medications, disease severity, clinical course, laboratory, and radiographic data at the time of histoplasmosis diagnosis from the medical records.

3 | CASE REPORTS

Six of 87 KTx recipients (6.9%), ages 11-18 years (median age 16 years), were diagnosed with disseminated histoplasmosis during the study period. Three of the six patients had received deceased donor transplants for FSGS. One patient with FSGS also had perinatally acquired HIV. Other comorbidities included VATER anomaly (n = 1), neurogenic bladder (n = 1), and medullary cystic kidney disease (n = 1). The median time from transplant to the diagnosis of histoplasmosis was 14.8 months (IQR 2.2-38.3). None of these patients had a history of transplant rejection prior to the diagnosis of histoplasmosis. Also, no patient had pretransplant *Histoplasma* testing and only one patient had antibody testing at the time of diagnosis.

Our cases had a variety of symptoms on presentation, but the majority of cases presented with fever, respiratory symptoms, and fatigue. BAL was done for diagnosis in four of the six cases. All patients recovered and there were no deaths. Possible relapse of disseminated histoplasmosis occurred in one patient following an acute rejection after her second KTx. All patients were placed on suppressive therapy of itraconazole 200 mg orally once daily, following treatment. All patients had near undetectable/undetectable antigen levels at the time of transitioning to suppressive therapy. Details of each patient's illness are outlined in Table 1 and the brief descriptions following.

3.1 | Case 1

A 16-year-old boy with well-controlled, perinatally acquired HIV received a deceased donor KTx for FSGS. At 2.4 months post-transplant, he presented with a 1-week history of fever, cough, malaise, vomiting, and weight loss. His CD4 count on admission was 17 cells/mm^3. His CD4 count prior to transplant was not available in the medical record, however, was presumed to be <50 in the immediate post-transplant period as he was on MAC prophylaxis with azithromycin. In addition, he was not on itraconazole prophylaxis prior to his transplant-related immunosuppression. Soon after admission he developed respiratory distress requiring supplemental oxygen and had a BAL with cytology. Silver stain revealed organisms consistent with histoplasmosis. In addition, both urine and serum *Histoplasma* antigen tests were elevated above the upper limit of quantification. He was initially treated with liposomal amphotericin B and then transitioned to itraconazole for rising serum creatinine. He was transitioned back to thrice weekly amphotericin B when he developed transaminitis. After resolution, he was restarted on itraconazole with improvement in his serum and urine antigens. Indefinite suppressive therapy with itraconazole was continued following his treatment course.

3.2 | Case 2

An 11-year-old girl received a deceased donor KTx for FSGS. She presented at 1.6 months post-transplant with a 3-week history of intermittent fever, fatigue, dry cough, and frontal headache. Her urine *Histoplasma* antigen was positive at 14.3 ng/mL. She was treated with itraconazole but was transitioned to voriconazole for repeatedly low serum itraconazole levels felt to be due to both poor compliance and poor absorption. While she had an uncomplicated clinical course, she continued to be noncompliant with both immunosuppressive and antifungal therapy, and as a result, she had three episodes of acute rejection and repeat KTx 11 years after her first. She did not receive antifungal prophylaxis or therapy in the time preceding or following her second transplant due to negative serum *Histoplasma* antigen and negative complement fixation antibody testing done at that time (despite poor compliance with her initial treatment course). Three years following her second transplant, at the age of 24, she presented with cutaneous lesions, and GMS showed *Histoplasma* which was also detected in culture of the biopsy specimen. A urine *Histoplasma* antigen done concurrently was above the upper limit of quantification, and serum antigen was 8.39 ng/mL. She was restarted on itraconazole for possible relapsed disease, with resolution of her skin lesions and improvement in serum and urine *Histoplasma* antigens. She remains on indefinite suppressive antifungal therapy.

3.3 | Case 3

An 11-year-old girl received a KTx for renal anomalies associated with VATER syndrome. She presented at 82.1 months post-transplant with a 2-week history of fever, fatigue, dry cough, abdominal pain, and weight loss. She had progressive illness with pancytopenia and hypoxia requiring

Table 1 Diagnostic labs, imaging and medications for prophylaxis treatment and immune suppression in pediatric kidney transplant recipients with histoplasmosis

Patient	Induction	Post-transplant fungal prophylaxis	Post-transplant immuno-supression	Tacrolimus level[c] (ng/mL)	Histoplasma antigen (ng/mL)	Evidence of dissemination	Imaging findings	Treatment	Length of treatment	Suppressive therapy
1	Thymoglobulin® High dose steroids	Nystatin POD[a] 0-16	Tacrolimus Mycophenolate mofetil Prednisone[b]	10.4	Urine: ALQ[d]	Cytopenias[e] Constitutional symptoms	CXR: Diffuse nodules with left perihilar infiltrates	Liposomal Ampho B[f] Itraconazole	2 wk 12 mo	Itraconazole
2	Thymoglobulin® High dose steroids	Diflucan POD 1-8	Tacrolimus Mycophenolate Mofetil prednisone	7.8	Urine: 14.3	Splenomegaly Constitutional symptoms	CT thorax: Left lung infiltrate. No enlarged lymph nodes.	Itraconazole Voriconazole	2 wk 12 mo	Voriconazole
3	Thymoglobulin® High dose steroids	Diflucan 3 mo	Tacrolimus Mycophenolate Mofetil prednisone	7	Urine: 17.06	Pancytopenia	CT Chest/Abd: Diffuse, ground-glass opacities mediastinal & hilar nodes, splenomegaly	Liposomal Ampho B Itraconazole	2 wk 12 mo	Itraconazole
4	Thymoglobulin® High dose steroids	Nystatin POD 1-5	Tacrolimus Mycophenolate mofetil Prednisone	4.0	Urine: ALQ Pericardial fluid: 4.86 Blood: ALQ	Pancytopenia	CXR: Cardiomegaly with pulmonary edema, small bilateral pleural effusions	Liposomal Ampho B Voriconazole Itraconazole	10 days 10 days 12 mo	Itraconazole
5	Thymoglobulin® High dose steroids	Nystatin POD 2-4	Tacrolimus Mycophenolic acid Prednisone	10.5	Urine: 10.69	Cytopenias	CT chest: 2 non- calcified nodes in left lower lobe, large mediastinal nodes	Itraconazole	12 mo	Itraconazole
6	Thymoglobulin®	Nystatin POD 2-4	Tacrolimus	11.8	Urine: ALQ Blood: ALQ	Severe GI symptoms	CT chest: Bilateral airspace disease lower lobes,paratracheal lymph nodes	Liposomal Ampho B Itraconazole	20 days 12 mo	Itraconazole

[a]Post op day. [b]Patient was not on prednisone at the time of histoplasmosis diagnosis. [c]Levels were drawn on admission at the time of histoplasmosis diagnosis. [d]Above the upper limit of quantification. [e]Anemia and thrombocytopenia. [f]Amphotercin B.

noninvasive ventilation. BAL revealed organisms consistent with *H. capsulatum* on cytopathology. Urine *Histoplasma* antigen was positive at 17.06 ng/mL. She also had antibody testing which showed a weakly positive complement fixation for the yeast phase of the fungus at 1:8 and negative immune diffusion. She completed a 14-day course of amphotericin B and was transitioned to itraconazole. Long-term suppressive therapy with itraconazole was continued following the course of treatment.

3.4 | Case 4

A 16-year-old girl with a history of myelomeningocele and ESRD secondary to neurogenic bladder received a deceased donor renal transplant. She presented at 23.7 months post-transplant with a 3-day history of fever, vomiting, and diarrhea and a 1 kg weight loss over the course of approximately 1 month. She developed pancytopenia, respiratory distress, and an enlarged cardiac silhouette on chest radiograph. Echocardiogram revealed pericardial effusion with tamponade. She had urgent pericardiocentesis as well as BAL. Both pericardial fluid and BAL were *Histoplasma* antigen-positive. Both serum and urine *Histoplasma* antigens were positive above the upper limit of quantification. She was initially treated with amphotericin B and transitioned to itraconazole. She had a complicated course with immune reconstitution inflammatory syndrome requiring prolonged, high-dose prednisone. She was treated for just under a year before transitioning to adult care and was lost to follow-up.

3.5 | Case 5

An 18-year-old girl received a deceased donor transplant for FSGS. She presented at 14 months post-transplant with a 2-week history of fever, chest pain, weight loss, malaise, headache, and myalgias. Her urine *Histoplasma* antigen was positive at 10.69 ng/mL. After a brief, uncomplicated hospitalization, she was started on itraconazole to complete a course of therapy and remains on lifelong suppressive therapy with the same agent.

3.6 | Case 6

An 18-year-old girl with a history of hereditary amaurosis of Leber and medullary cystic disease received a deceased donor renal transplant. She presented at 15.5 months post-transplant with a 2-week history of fever, cough, vomiting, and diarrhea. She developed unexplained hypoxia and lung disease necessitating a BAL which was positive for *H. capsulatum* by culture. *Histoplasma* urine and serum antigens were both above the upper limit of quantification. She was started on amphotericin B. She was transitioned to itraconazole and completed 12 months of treatment followed by suppressive therapy.

4 | DISCUSSION

We describe our experience with histoplasmosis after KTx in six children in Memphis, TN, a *Histoplasma* endemic area. Among 87 KTx performed over 14 years, we found an attack rate of 6.9 per 100 cases of histoplasmosis. Comparatively, reports from adult KTx programs in *Histoplasma* endemic areas have reported rates of disseminated disease at 0%-2.1%. Cuellar Rodriguez et al in the largest single-center study on the subject to date reported an incidence of one case per thousand patient years which is similar to the reported global incidence.[9] The median time to infection in our case series of 14.8 months was slightly earlier than that reported in adult studies, but most cases still occurred within the first 2 years post-transplant which is similar to previous studies in adult populations.[7,9]

In endemic regions of the country, histoplasmosis seems to occur with low frequency but at higher rates in our pediatric SOT population when compared with adults. However, a high index of suspicion and early treatment appears to portend a good prognosis. Clinical presentation in our cases was variable but most cases presented with unexplained fever, fatigue, and respiratory symptoms. Most patients progressed quite rapidly shortly after admission to requiring oxygen supplementation and a higher level of care. A diagnosis of *Pneumocystis* infection was considered in several children. Clinicians in endemic areas should have a low threshold to evaluate and treat for histoplasmosis in immunosuppressed children with similar symptoms. Histoplasmosis antigen assays in urine, serum, and BAL were the highest yield diagnostic procedures in our patient population, and BAL with GMS staining yielded the most rapid results.

The treatment approach at our institution was variable based on patient tolerance and adverse reactions. A few of our patients were diagnosed prior to the IDSA histoplasmosis treatment guidelines which further explain treatment variations. Our current treatment protocols are tailored to each patient based on tolerability, limiting side effects while preserving the efficacy of treatment. We often incorporate liposomal amphotericin B followed by itraconazole 200 mg orally twice a day for at least 12 months in moderate-to-severe disease.[10] However, given the nephrotoxicity of amphotericin B and the tenuous renal function in this vulnerable population, we often initiate therapy with itraconazole in patients with milder disease. Several patients presented with fever and mild lung disease, and it was deemed safe to start with itraconazole as rapid reduction in fungal burden was not necessary.

Another management consideration is the interaction between azoles and immunosuppressive agents. Azoles increase serum concentrations of cyclosporine, tacrolimus, and sirolimus. This portends the need for close monitoring of these drug levels during initiation and discontinuation to prevent drug toxicity and graft rejection.[11-15] Furthermore, children have more rapid clearance of azoles necessitating higher and more frequent dosing.[13,15] Thus, it is often challenging to balance appropriate immunosuppression with efficacious antifungal therapy. Previous studies suggest halving the dose of tacrolimus at the onset of therapy for histoplasmosis in SOT recipients along with frequent drug monitoring to guide further tacrolimus dosing while on azole therapy.[12] Another observed challenge comes with medication compliance due to side effects and is a mitigating factor in addressing the issue of adherence to prophylaxis/treatment protocols.

With regard to the duration of suppressive therapy following histoplasmosis treatment, our current practice is to continue with indefinite suppression in conjunction with obtaining interval *Histoplasma* antigen levels. Thus far, we have had good success with this approach having only one reported case of possible relapse. However, challenges including medication and follow-up compliance remain evident.

In summary, our case series highlights that histoplasmosis is an important clinical consideration in pediatric KTx patients living in *Histoplasma* endemic areas. Having a low threshold for urine antigen testing in patients with febrile respiratory illnesses can lead to prompt diagnosis with early therapy resulting in a good clinical response. *Histoplasma* antigen testing in blood and urine is an important diagnostic and prognostic tool, and may have a valuable role in screening in these high-risk patients; however, BAL with GMS staining of fluid is the most rapid way to make the diagnosis as antigen assays are only performed in specialized laboratories. While it is apparent that treatment should continue until antigenemia is resolved, the duration of secondary prophylaxis needs to be better defined. Further studies are also needed to evaluate the benefit of screening asymptomatic KTx patients living in *Histoplasma* endemic regions.

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