

ABSTRACT

Background: Histoplasmosis in transplant recipients is understudied. We reviewed a large cohort of histoplasmosis in patients with solid organ and stem cell transplants in an endemic area to describe the epidemiology, clinical findings, and outcomes.

Methods: We performed a single-center retrospective cohort study of patients diagnosed with histoplasmosis between 2002 and 2017. Demographic data, clinical findings, diagnostic methods, treatment, and mortality were collected. We compared the characteristics of patients with history of transplant to non-transplant (NT) patients.

Results: We identified 261 patients with histoplasmosis. Of those, 28(11%) were transplant recipients; 8(29%) liver, 8(29%) lung, 6(21%) kidney, 3(11%) heart, and 3(11%) stem cell. Median time from symptom onset to diagnosis was 6 vs 34 days in transplant vs NT groups (p=0.001). Lung was the most common organ involvement (89% in transplants vs 78% in NT, p=0.168). Spleen involvement was more commonly found in transplant (29 vs 14%, p=0.039). In patients with disseminated disease, urine antigen was 100% sensitive in transplant compared to 78% in the NT group (p=0.038). Duration of treatment was 13 vs 6 months in transplant vs NT patients (p= 0.003). Mortality was comparable between groups (14 vs 15% in transplant vs NT, p=0.918). Median time from transplant to diagnosis was 4.21 years. However, five patients (18%) developed histoplasmosis within 6 months. For these early diagnosed patients, ICU admission rate was 80 vs 30% (p=0.04) and rate of mechanical ventilator use was 80 vs 22% (p=0.011) compared to patients diagnosed later.

Conclusion: Transplant recipients with histoplasmosis are likely to be diagnosed early and treated longer. Urine antigen is highly sensitive for diagnosis of disseminated disease in transplants. Histoplasmosis that occurs within the first 6 months after transplantation tends to be more severe.

BACKGROUND

- *Histoplasma capsulatum* is a dimorphic fungus that resides in the soil of certain regions of the USA, particularly in the Ohio and Mississippi River Valleys.
- Patients with defect of cell-mediated immunity including transplant recipients are more vulnerable than immunocompetent patients and more frequently develop disseminated disease and die from the infection
- In transplant population, the incidence of histoplasmosis is 0-2.1% with overall mortality of 9-11 %. Disseminated disease found in 33-64%.
- We reviewed a cohort of histoplasmosis in patients with solid organ and stem cell transplants in a large transplant center in an endemic area to better understand the epidemiology and outcomes of histoplasmosis in patients with transplants.

METHODS

- **Design:** Retrospective cohort from Barnes-Jewish Hospital, a 1,250 bed academic medical and transplant center in St. Louis, MO
- **Study period:** January 1, 2002 through December 31, 2017
- **Inclusion criteria:** New diagnosis of histoplasmosis in patients age \geq 18 years with solid organ or hematopoietic stem cell transplant (HSCT)
- **Exclusion criteria:**
 - False positive histoplasma antigen
 - No evidence of active histoplasmosis
 - Presumed ocular histoplasmosis (POHS)
 - Fibrosing mediastinitis
 - ICD code without medical data to support diagnosis
 - Insufficient clinical data
 - Cases with initial diagnosis before study period
- **Statistical methods:** performed using SPSS v25.0, p<0.05 considered significant

RESULTS

Table 1 Patient Characteristics

Patient characteristics	Transplant N=28 (%)	Non-transplant N=233 (%)	p-value
Age, years (median, IQR)	54 (33,62)	50 (36, 62)	0.855
Male sex	17 (61)	139 (60)	0.914
Race			0.481
White	24 (86)	173 (74)	
African American	2 (11)	48 (21)	
Other	1 (4)	7 (3)	
Unknown	1 (4)	5 (2)	
Symptoms			
Cough	17 (61)	92 (39)	0.096
Fever	15 (54)	112 (48)	0.818
Dyspnea	14 (50)	86 (37)	0.373
Gastrointestinal symptoms	11 (39)	73 (31)	0.663
Night sweat	7 (25)	47 (20)	0.793
Weight loss	5 (18)	75 (32)	0.252
Chest pain	1 (4)	52 (22)	0.055
Skin nodules	1 (4)	2 (1)	0.397
Asymptomatic lung nodule(s)	1 (4)	24 (10)	0.069
Days from symptom onset to diagnosis, days, median (IQR)	16 (10,33)	34 (17, 101)	0.001

Table 2 Organ involvement

Organ involvement	Transplant N=28 (%)	Non-transplant N=233 (%)	p-value
Lung	25 (89)	182(78)	0.168
Blood	7 (25)	47(20)	0.551
Spleen	8 (29)	32 (14)	0.039
Liver	4 (14)	24 (10)	0.520
Gastrointestinal tract	3 (11)	8 (3)	0.079
Skin	1 (4)	12 (5)	0.826
Central nervous system	1 (4)	12 (5)	0.717
Adrenal gland	1 (4)	7 (3)	0.869
Lymph node	-	20 (9)	0.236
Oral cavity	-	11 (5)	0.233
Bone marrow	-	23 (10)	0.190
Others	-	8 (3)	0.319
Disseminated disease	18 (64)	116 (50)	0.147
Time from transplant to diagnosis, years, median (range)	4.21 (0.02 – 19.33)	-	
Diagnosis of histoplasmosis in the first six months of transplant	5 (18)	-	

Table 3 Diagnostic test positivity

Diagnostic method	Test positivity		p-value
	Transplant N (%)	Non-transplant N (%)	
Isolated pulmonary disease	10 (36)	117(50)	
Urine antigen	4/8 (50)	37/81 (46)	0.815
Serum antigen	1/1 (100)	7/12 (58)	0.411
Antibody	3/7 (43)	41/60 (16)	0.179
Disseminated disease	18 (64)	116(50)	
Urine antigen	16/16 (100)	75/96 (78)	0.038
Serum antigen	6/7 (86)	13/20 (65)	0.302
Antibody	5/9 (56)	33/52 (63)	0.651

Table 4 Antifungal treatment

Antifungal agent	Transplant N = 28 (%)	Non-transplant N = 233 (%)	p-value
Primary treatment			
Amphotericin B lipid formulation	13 (46)	82 (35)	0.485
Itraconazole	11 (39)	104 (45)	0.842
Voriconazole	2 (7)	9 (4)	0.414
Fluconazole	-	7 (3)	0.353
Posaconazole	1 (4)	-	0.004
No antifungal/early death	1 (4)	31 (13)	0.150
Subsequent treatment^a	19 ^b	99 ^b	0.110
Itraconazole	12 (63)	62 (62)	0.965
Voriconazole	1 (5)	8 (8)	0.649
Posaconazole	1 (5)	1 (1)	0.188
Isavuconazole	-	2 (2)	0.532
No antifungal/early death	5 (26)	26 (27)	0.301
Median duration of treatment (months)	13.7	6.3	0.003

a: Follow amphotericin B

b: Number of patients received amphotericin B at any time

DISCUSSION

- Disseminated disease and mortality rate of transplant recipients with histoplasmosis are comparable to previous studies and not different from non transplant group
- Urine histoplasma antigen highly yields positivity in transplant patients with disseminated disease indicating high burden of disease
- Nearly one third of transplant recipients with histoplasmosis develop infection within the first year of transplant suggesting donor-derived infection or reactivation
- Histoplasmosis that occurs within the first 6 months tends to be more severe. Perhaps related to higher level of immunosuppression
- Majority of patients in both transplant and non transplant groups received either lipid formulation of amphotericin B or itraconazole depending on severity, but duration of treatment was significantly longer in transplant group
- Results of this study are limited by retrospective nature. Difference between transplant recipients and non transplant patients may not be apparently appreciated since patients with HIV and other immunosuppression were included in non transplant group

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CONCLUSION

- Transplant recipients with histoplasmosis are likely to be diagnosed early and treated longer compared to non-transplant patients
- Urine histoplasma antigen is highly sensitive for diagnosis of disseminated disease in transplants
- Histoplasmosis that occurs within the first 6 months tends to be more severe