TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

LETTER TO THE EDITORS

Histoplasmosis in a lung transplant recipient from a nonendemic area

doi:10.1111/tri.12365

Dear Sirs,

We report a case of disseminated histoplasmosis in a 63-year-old lung transplant (LT) recipient in Italy. To our knowledge, this is the first autochthonous case documented in a solid organ transplant (SOT) recipient from a nonendemic area. *Histoplasma capsulatum* is endemic to certain parts of Central America and mid-western United States; in contrast, its presence as an autochthonous fungus in Europe is still controversial [1]. In Italy, the existence of *H. capsulatum* in soils has been described, predominantly in the Po valley area [2]. Around 40 cases of histoplasmosis have been reported in Italy since 1980, mainly among travelers returning from endemic areas and in human immunodeficiency virus (HIV)-infected patients [2]. Infection by *H. capsulatum* occurs more often in immunocompromised hosts with T-cell defects [3]. Nevertheless, while incidence rates of histoplasmosis can reach 5% in HIV-infected patients, a very low number of cases are reported among SOT recipients [3–6].

In our case, a male recipient of bilateral LT for sarcoidosis presented 11 years after transplant with a 4-week history of productive cough, progressive shortness of breath, and diarrhea. He worked as an industrial maintenance technician and resided in northeast Italy (Veneto and Friuli Venezia Giulia regions), without reporting any travel abroad before or after LT. At presentation, his immunosuppressive regimen included tacrolimus (0.5 mg BID), mycophenolate mofetil (1 g BID), and prednisone (15 mg/day). A chest CT scan revealed a nodular consolidation in the right upper lobe, multiple diffuse bilateral patchy lung opacities, and mediastinal lymphoadenopathies. Laboratory tests showed acute renal failure, pancytopenia with lymphopenia (260 cells/mmc), increased LDH levels, and a low PaO_2/FiO_2 ratio (200 mmHg). Septic disseminated intravascular coagulation (DIC) was suspected due to hemolytic anemia, decreased fibrinogen levels, and increased procalcitonin. The patient was placed on an antimicrobial regimen of meropenem, amikacin, and linezolid. Immunosuppression was reduced and methylprednisone was added due to severe respiratory distress. A repeat CT scan showed a worsening of disseminated micronodular lesions and increased chest consolidations. At hospital day 7, he was transferred to the intensive care unit and intubated. Caspofungin was empirically started and switched within 48 h to liposomal amphotericin B (5 mg/kg/day) to extend antifungal coverage. Bronchoalveolar lavage (BAL) was negative for *Pneumocystits jirovecii* oocystis, while galactomannan (GM) antigen was positive in three consecutive determinations (6.9, 4.1, and 4.8 respectively). BAL and bone marrow (BM) samples grew yeast forms morphologically consistent with *H. capsulatum*. White, cottony colonies developed on Sabouraud's dextrose agar. Nucleotide sequence analysis identified *H. capsulatum var. capsulatum*. Despite antifungal therapy and aggressive resuscitation measures, the patient progressed to multi-organ failure and died after 25 days of hospitalization.

Our report can be classified as a proven case of disseminated histoplasmosis. In fact, both compatible clinical manifestations and microbiological evidence of *Histoplasma* in BAL and BM were seen. The disease acquisition was probably due to post-transplant environmental exposure. Late presentation after LT, disease severity, and BM culture positivity were distinctive features of our report.

As summarized in Table 1, only 10 cases of histoplasmosis in lung transplant (LT) recipients from five centers across the United States have been published to date [5–7]. Although histoplasmosis has been reported mainly in liver and kidney transplants, differences in prevalence among SOT groups are noticeable [4–6,8]. Three out of 14 cases (21%) were reported in LT recipients over a period of 10 years from the Cleveland Clinic [5]. Afterward, a multicenter study encompassing 152 cases of histoplasmosis in SOT reckoned nine cases (5%) in LT recipients [6]. In various studies including SOT recipients, histoplasmosis showed a median time from transplant to diagnosis between 10.5 and 17 months [4–6,8]. Early post-transplant presentation correlated with poor outcomes [6]. Mortality rates ranged from 0 to 13%, with most deaths occurring within the first 3 weeks following diagnosis [5,6,8]. Compared with the above-mentioned case series, Table 1 evinces higher mortality rates (3/11, 27%) and a longer median time to histoplasmosis presentation (57 months,

Table 1. Review of published cases of histoplasmosis in lung transplant recipients and summary of current case.

Source	Age/Sex	Time post-LT (months)	Country	Regimen	Urine/ Serology	Histology/ Culture	Treatment	Outcome
Cuellar-Rodriguez	41/M	10	OH (US)	CyA, Pr, MMF	+/–	+/ND	AmB, Vor	Cured
et al. [5]	52/M	47	OH (US)	SIR, Pr, MMF	–/ND	+/ND	AmB, Itr	Cured
	64/M	83	OH (US)	AZA, Pr, CyA	+/+	+/+	AmB, Vor	Expired†
Shah *et al.* [7]	43/M	10*	OH (US)	ND	–/–	+/+	Itr, Vor	Cured
Assi *et al.* [6]	59/M	23	AL (US)	CyA, MMF, Pr	+/ND	+/+	AmB, Itr	Dead after relapse
	29/M	84	MN (US)	CyA, MMF, Pr	+/ND	+/+	AmB, Itr/Vor	Expired†
	59/F	57	IN (US)	MMF, Pr	+/ND	ND/+	AmB, Itr	Expired†
	49/F	144	IN (US)	SIR, Pr	+/–	ND/–	AmB, Itr/Pos	Cured
	67/F	41	IN (US)	CyA, MMF, Pr	+/–	–/–	Itr	Cured
	68/M‡	96	IA (US)	CyA, MMF, Pr	+/ND	ND/–	AmB, Itr	Expired at day 7
Our case	62/M	124	Italy	TAC, Pr, MMF	ND/ND	ND/+	AmB	Expired at day 25

LT, lung transplant; CyA, cyclosporine A; TAC, tacrolimus; Pr, prednisone; MMF, mycophenolate mofetil; SIR, sirolimus; AZA, azathioprine; Amb, amphotericin B; Vor, voriconazole; Itr, itraconazole; Pos, posaconazole.

*Donor-derived transmission.

†Death for causes not related to *Histoplasma* infection.

‡Patient receiving kidney and lung transplants.

range 10–144) in LT compared with other SOT. A delay in disease presentation for LT recipients could be postulated due to the widespread use of antifungal prophylaxis after LT [5].

A prompt diagnosis of histoplasmosis requires reliable diagnostic tests. While serology is rarely useful, tests for antigens are frequently positive (Table 1) [1,5,6]. However, antigen detection is not available in all countries and is not performed at our center. Microbiological cultures can be helpful: rates of *Histoplasma* isolation from BAL and blood cultures yielded positive results in 55% of LT. BM cultures, taken to investigate the cause of pancytopenia, were indicative of Histoplasma infection in LT in only one other case [5]. Amphotericin B (AmB), which is often initiated in severe cases until clinical stability is reached [9], was used in 80% of LT recipients (Table 1).

The management of histoplasmosis in SOT can be challenging, especially in areas where physicians are less familiar with the recognition of the disease. Due to the paucity of known cases, the Infectious Diseases Society of America (IDSA) guidelines did not include recommendations specific to this patient population [9]. In addition, features of histoplasmosis may contribute to a delay in the correct diagnosis: clinical manifestations can occur late after transplant and be prolonged and nonspecific, laboratory and radiological results may be similar to other opportunistic infections, and microbiological tests, such as *Aspergillus* GM, can be falsely positive [10]. As *Aspergillus* causes the majority of lung infections in LT, less common fungi are still hardly considered in the differential diagnosis. Thus, histoplasmosis might be underdiagnosed and underestimated in this group.

For these reasons, a timely diagnosis through laboratories with mycological expertise and a prompt start of an adequate antifungal treatment should be undertaken if histoplasmosis is suspected. Furthermore, due to the severity of the disease in LT recipients, antifungal prophylaxis is advocated. Finally, as atypical and delayed presentations are not infrequent, a high level of vigilance and a strict epidemiological surveillance should be maintained for SOT recipients in those areas where the disease occurrence is less expected.

Elda Righi,[1] Manuela Lugano,[2] Maha Assi,[3] Assunta Sartor,[4] Elena De Carolis ,[5] Massimo Crapis,[1] Barbara Cadeo,[1] Antonietta Vella,[5] Maurizio Sanguinetti,[5] Claudio Scarparo,[4] Giorgio Della Rocca,[2] and Matteo Bassetti[1]

1 Infectious Diseases Division, Santa Maria della Misericordia University Hospital, Udine, Italy

2 Department of Anesthesia and Intensive Care Medicine, Santa Maria della Misericordia University Hospital, Udine, Italy

3 Department of Internal Medicine, University of Kansas School of Medicine, Wichita, KS, USA

4 Microbiology Division, Santa Maria della Misericordia University Hospital, Udine, Italy

5 Institute of Microbiology, Università Cattolica del Sacro Cuore, Rome, Italy

e-mail: elda.righi@libero.it

Funding

No funding.

References

1. Cano MV, Hajjeh RA. The epidemiology of histoplasmosis: a review. *Sem Respir Infect* 2001; **16**: 109.
2. Manfredi R, Mazzoni A, Nanetti A, Chiodo F. Histoplasmosis capsulati and duboisii in Europe: the impact of the HIV pandemic, travel and immigration. *Eur J Epidemiol* 1994; **10**: 675.
3. Farina C, Rizzi M, Ricci L, Gabbi E, Caligaris S, Goglio A. Imported and autochthonous histoplasmosis in Italy: new cases and old problems. *Re Iberoam Micol* 2005; **22**: 169.
4. Vail GM, Young RS, Wheat LJ, Filo RS, Cornetta K, Goldman M. Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. *Transpl Infect Dis* 2002; **4**: 148.
5. Cuellar-Rodriguez J, Avery RK, Lard M, *et al.* Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. *Clin Infect Dis* 2009; **49**: 710.
6. Assi M, Martin S, Wheat LJ, *et al.* Histoplasmosis after solid organ transplant. *Clin Infect Dis* 2013; **57**: 1542.
7. Shah SS, Karnak D, Shah SN, *et al.* Broncholith caused by donor-acquired histoplasmosis in a lung transplant recipient. *J Heart Lung Transpl* 2007; **26**: 407.
8. Grim SA, Proia L, Miller R, *et al.* A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. *Transpl Infect Dis* 2012; **14**: 17.
9. Wheat LJ, Freifeld AG, Kleiman MB, *et al.* Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007; **45**: 807.
10. Vergidis P, Walker RC, Kaul DR, *et al.* False-positive Aspergillus galactomannan assay in solid organ transplant recipients with histoplasmosis. *Transpl Infect Dis* 2012; **14**: 213.