



Original Article

Infectious diseases in solid organ transplant recipients: Analysis of autopsied cases in Japan

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ABSTRACT

Background: With the improvements in immunosuppressive agents and graft survival, infections such as mycoses have become major complications after solid organ transplantation (SOT).**Methods:** Our group has continuously updated an epidemiological database of visceral mycoses (VM) among autopsy cases in Japan since 1989. Data on infectious agents and clinical information were compiled using similar procedures.**Results:** Among the all autopsied cases studied, 356 undergone SOT. Of these, 214 (60.1%) suffered from one or more types of infections, including 51 (14.3%) with VM. Thus, the incidence of VM was higher in SOT recipients than in non-transplanted cases ($P < 0.0001$). *Aspergillus* spp. (*Asp*) was the most predominant agent and *Candida* spp. was second. Specifically, among SOT recipients, *Asp* was the most predominant in liver and lung transplant recipients. Among the 217 autopsied liver transplants cases, the incidence of VM was highest in those with fulminant hepatitis (FH, $P = 0.01$). The incidence of cytomegalovirus infection tended to be higher in cases with mycosis ($P = 0.06$). Multivariate logistic regression analysis identified FH (odds ratio, 3.61, 95% confidence interval 1.34–9.75; $P = 0.03$) as an independent risk factor for mycosis in liver transplant recipients.**Conclusion:** This epidemiological analysis of autopsied cases provides a strong incentive to intensify efforts to diagnose and treat post-SOT infectious diseases.

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1. Introduction

Over the past 30 years, solid organ transplantation (SOT) has become established as an accepted therapy for end-stage disease of the kidneys, liver, heart, and lungs [1]. In Japan, SOTs were mainly performed using living related donors until the Organ Transplant Law went into effect in 1997. This law allowed transplants from brain-dead donors and was further revised in 2010 to allow transplantation in the absence of the donor's prior written informed consent, if the donor's family approved. As a result, heart

transplantation rates have also increased since then [2]. Transplants of approximately 1300 kidneys [3], 400 livers [4], 37 hearts [2], 40 lungs [5], 30 pancreases and pancreas islets [6,7], and small intestines [8,9] were performed in 2013. Between 2005 and 2012, transplantations of approximately 3800 livers [4], 10,500 kidneys [3], 120 hearts [10], 300 lungs [5], 15 small intestine grafts [9], and 125 pancreases [7] were performed in Japan.

With improvements in immunosuppressive agents and graft survival, infections, such as mycoses, viral infections [1,11], and malignancies [12] have become the major post-SOT complications. As a result of the growing number of immunosuppressed patients experiencing prolonged survival, an increased incidence of serious opportunistic infections is being seen. Several investigators [1,11,13,14] have published data on fungal [13,15] and other types

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infections following SOT, but only limited autopsy data from SOT recipients are available, so far.

Our group has continuously updated an epidemiological database of visceral mycosis (VM) occurrences among autopsy cases in Japan, beginning from 1989 [16–19]. VM is especially challenging in patients with a higher risk of infection.

Here, we report on autopsied cases demonstrating infectious events, especially mycosis, after SOT in Japan. This is the first report providing nationwide survey data from SOT recipients with infections in Japan.

2. Material and methods

2.1. Data collection

Data on solid organ transplantations, conducted between 2005 and 2012, were extracted from the Japanese Society of Pathology's "Annual of Pathological Autopsy Cases in Japan". Cases involving stillborn babies and cases under investigation were excluded.

Data on the involved infectious agents, such as bacteria, fungi, viruses, parasites, and unidentified agents, were compiled following our published procedures regarding our VM data [16,18,19]. In this analysis, two or more infectious agents identified in the same autopsied case, were counted as one case with multiple events. Bacterial, fungal, and viral infections were recorded if those types of events or named agents were encoded; unidentified infection was recorded only if just "infection" was recorded, or if an infection was suggested based only on clinical information, such as pneumonia or peritonitis, in the autopsy record. As in our previous reports [16–19], pneumocystis pneumonia was excluded from the mycoses in accordance with the recorded definition.

All diagnoses were made by the institutional pathologists.

Clinical characteristics were compiled including sex, age, transplant type, underlying disease resulting in SOT, hepatitis C virus (HCV) and hepatitis B virus (HBV) status, cytomegalovirus (CMV) infection after SOT, survival time after SOT, and other factors. Survival after SOT was described as either acute or chronic to indicate patient death <3 months or >3 months following SOT, respectively.

2.2. Statistics

Continuous variables are presented as the median values (25th, 75th percentiles) and were compared using the Wilcoxon's test.

Numerical variables are provided as N (%) and were assessed using Pearson's chi-square test or Fisher's exact test, as appropriate.

Multivariate logistic regression analyses were used to estimate the independent risk factors for mycosis by adjusting for age, fulminant hepatitis (FH), hepatocellular carcinoma (HCC) and CMV infection.

All reported *P*-values are two sided; a *P*-value < 0.05 was considered statistically significant. Analyses were performed using SPSS software, version 23.0 (SPSS, Chicago, IL).

3. Results

3.1. General information

Between 2005 and 2012, a total of 87,226 cases were autopsied. Among them, 356 patients had undergone SOTs of the liver (n = 217), kidney (n = 112), lung (n = 13), heart (n = 9), and other organs (n = 5) (Table 1); VM was identified in 51 (14.3%) cases. Thus, the incidence of VM after SOT was higher than in cases not undergoing SOT (*P* < 0.0001).

Of 356 SOT cases, 214 (60.1%) demonstrated at least one type of infectious agent; mycoses were identified in 51 (14.3%) cases, bacterial infections in 26 cases, and viral infections in 26 cases. More than two types of infectious agents were described in 23 autopsy cases.

A total of 245 infectious events was observed, including fungal infection (N = 55), bacterial infections (26; e.g., methicillin-resistant *Staphylococcus aureus* or tuberculosis), and 27 viral infection (e.g., CMV or disseminated varicella); other infection types included entamoebiasis and pneumocystis pneumonia. The incidence of mycosis was significantly higher than bacterial or viral infections (both *P* < 0.0001) (Table 2).

3.2. Infectious events according to the type of transplanted organ type (Table 3)

Recipients' characteristics, such as age, sex, and post-transplant survival, were significantly different for each transplanted organ type. Furthermore, there were infectious events differences, e.g., viral (*P* < 0.0001) and bacterial infections (*P* = 0.006) between organs types; however, no organ-related difference was observed for mycosis. The number of infectious events per case was highest among lung transplant recipients.

Table 1
Annual frequency of autopsied cases with solid organ transplantation (References [16–19]).

	Year								Total
	2005	2006	2007	2008	2009	2010	2011	2012	
All autopsied cases	18,924	17,733	16,384	15,764	13,787	13,482	12,339	12,310	87,226 ^b
Cases with VM	872 (4.6)	ND	720 (4.4)	ND	633 (4.6)	624 (4.6)	608 (4.9)	570 (4.6)	4027 ^c (4.6)
Total autopsied cases with SOT Transplants	58	53	48	50	28	40	41	38	356/87,226 (0.4)
Liver	34	33	30	28	19	18	32	23	217/356 (61.1)
Kidney	20	17	17	21	9	16	4	8	112/356 (31.5)
Heart	4	0	0	0	0	1	1	3	9/356 (2.5)
Lung	0	3	1	1	0	2	4	2	13/356 (3.7)
Small intestine	0	0	0	0	0	0	0	2	2/356 (0.6)
Pancreas	0	0	0	0	0	1	0	0	1/356 (0.3)
Others	0	0	0	0	0	2 ^a	0	0	2/356 (0.6)

SOT: solid organ transplantation. ND: not done. VM: visceral mycosis.

Numerical variates are given as N (%) and are compared with the chi-square test or Fisher's exact test, as appropriate.

^a Cases with double transplants of pancreas and kidney, and heart and kidney.

^b Total of autopsied cases in 2005, 2007, 2009, 2010, 2011 and 2012.

^c Total of cases with visceral mycosis in 2005, 2007, 2009, 2010, 2011, 2012.

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