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Surgery for Pulmonary Fungal Infections Complicating Hematological Malignancies

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Background: The complication rate of fungal disease is higher among patients with hematological malignancies. We investigated the clinicobacteriological outcomes of resected pulmonary fungal infections complicating hematological malignancies. **Methods:** Between 2001 and 2017, 21 patients with pulmonary fungal infections complicating hematological malignancies underwent resection, and their clinical records and survival were retrospectively reviewed. **Results:** The median age of the patients was 47 years, and 13 were male. The histological diagnoses were pulmonary aspergillosis (19 cases), mucormycosis (1 case), and cryptococcosis (1 case). The indications for surgery were resistance to antifungal therapy and the necessity of surgery before hematopoietic stem cell transplantation in 13 and 8 cases, respectively. The diagnoses of the hematological malignancies were acute myelogenous leukemia (10 cases), acute lymphocytic leukemia (5 cases), myelodysplastic syndrome (3 cases), and chronic myelogenous leukemia, malignant lymphoma, and extramedullary plasmacytoma (1 case each). The surgical procedures were partial resection (11 cases), segmentectomy (5 cases), lobectomy (4 cases), and cavernostomy (1 case). The size of the lesions was 0.9–8.5 cm. Fourteen cases had cavitation. There were no surgical-related deaths or fungal progression. **Conclusion:** Pulmonary fungal infections are resistant to treatments for hematological malignancies. Since the treatment of the underlying disease is extended and these infections often recur and are exacerbated, surgery should be considered when possible.

Key words: 1. Mycoses
2. Hematologic neoplasms
3. Thoracic surgery

Introduction

Invasive fungal infections (IFIs) associated with hematological malignancies are common (approximately 5%) [1] and have a high mortality rate. The risk of IFIs is high due to treatments for long-term neutropenia, such as chemotherapy for acute leukemia and hematopoietic stem cell transplantation (HSCT). IFIs represent various infectious diseases, although invasive pulmonary aspergillosis is the most common form of IFI [2]. Aspergillus may directly invade adjacent structures, including the blood vessels, or disseminate hematogenously. Other fungal organisms, including *Mucor* and *Scedosporium*, are also causes of fungal lung infections among immunocompromised patients. A definitive diagnosis is difficult to obtain, and many cases must be assessed based on clinical and radiographic findings alone. Antifungal

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drugs are generally used for treatment. However, if a fungal lesion is localized and resistant to antifungal agents, therapeutic pulmonary resection is indicated.

In recent studies, surgery has rarely been performed for IFIs in immunocompromised patients with hematological malignancies, because it may exacerbate leukemia and lymphoma. Even with improved tolerance to new, highly efficacious antifungal agents as first-line therapy (i.e., voriconazole) and prophylaxis (i.e., micafungin), mortality may be as high as 50% in neutropenic patients. However, surgery provides a definitive diagnosis, enables salvage therapy when medical treatment has failed, and represents the best opportunity to eradicate an IFI before HSCT.

The aim of the present study was to clarify the clinical outcomes of therapeutic and diagnostic pulmonary resection for IFIs complicating hematological malignancies.

Methods

Between January 2001 and December 2017, 21 patients underwent pulmonary resection for an IFI complicating a hematological malignancy at the Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital. A retrospective chart review of patients' clinical records was performed. This study was conducted with the approval of the Institutional Review Board. IFIs were suspected based on patients' clinical history and radiological findings, including chest X-rays and computed tomography (CT). Patients were diagnosed with or suspected to have an IFI after a detailed examination by bronchoscopy, bronchoalveolar lavage, and biopsy. All patients were treated with antifungal therapy before surgery, including various combinations of amphotericin B and azoles, as well as broad antibiotics. The following are surgical indications in our department: (1) controlled primary disease (white blood cell count $>2{,}000/\mu L$, neutrophils $>1{,}000/\mu L$); (2) no surgical risk factors, such as cardiopulmonary dysfunction or hepatorenal disorder; and (3) resistance to medical treatment and/or a curative target case before HSCT. We retrospectively reviewed clinicobacteriological findings. Overall survival and fungal progression following resection were calculated from the date of the surgical procedure and analyzed using the Kaplan–Meier method. Potential prognostic factors for overall survival were analyzed with the log-rank method and a Cox proportional hazards model. All p-values <0.05 were considered to indicate statistical significance. We used EZR ver. 1.35 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) for all statistical analyses.

Table 1. Characteristics of patients who underwent pulmonary resection for IFI (N=21)

Characteristic	Value
Age (yr)	47 (18–73)
Gender	
Male	13 (62)
Female	8 (38)
Hematological malignancy	
Acute myeloid leukemia	10 (48)
Acute lymphoblastic leukemia	5 (24)
Myelodysplastic syndrome	3 (14)
Chronic myeloid leukemia	1 (5)
Extramedullary plasmacytoma	1 (5)
Malignant lymphoma	1 (5)
Patients receiving HSCT	14 (67)
Timing of HSCT	
Before surgery	6 (29)
After surgery	7 (33)
Before and after surgery	1 (5)
Symptomatic	19 (90)
Most common symptom	
Fever	7 (33)
Chest pain	4 (19)
Cough	3 (14)
Hemoptysis	3 (14)
Dyspnea	2 (10)
Indications for surgery	
Resistance to antifungal therapy	13 (62)
Necessity of surgical treatment before HSCT	8 (38)
Duration of antifungal therapy (mo)	1–31
Details of antifungal therapy	
Amphotericin B	10 (48)
Voriconazole	8 (38)
Itraconazole	7 (33)
Miconazole	2 (10)
Micafungin	2 (10)
Fluconazole	2 (10)
Patients with cavitation on computed tomography	15 (71)
Patients with proven IFI	7 (33)

Values are presented as median (range), number (%), or range.
IFI, invasive fungal infection; HSCT, hematopoietic stem cell transplantation.

Results

In Table 1, the clinicobacteriological characteristics of the IFIs, including the relevant diagnostic data, are shown. The median age of the patients was 47 years, and 13 were male. The indications for surgery were resistance to antifungal therapy in 13 cases and the necessity of surgical treatment before HSCT in 8 cases. The most common hematological malignancy was acute myelogenous leukemia in 10 patients (48%), followed by acute lymphocytic leukemia in 5 (23.8%), myelodysplastic syndrome in 3 (14%), and chronic myelogenous leukemia, malignant lymphoma, and extramedullary plasmacytoma in 1 each (5%). Fourteen patients (67%) received HSCT. Of these patients, 6 (43%) received a transplant before surgery, 7 (50%) received a transplant after surgery, and 1 (7%) received a transplant both before and after surgery. Persistent fever higher than 38.0°C was the most common presenting symptom in 7 patients (33%), followed by chest pain in 4 (19%), cough in 3 (14%), hemoptysis in 3 (14%), and dyspnea in 2 (10%). The median duration of antifungal therapy before surgery was 2 months (range, 1–31 months), and we prescribed amphotericin B in 10 cases (48%), voriconazole in 8 (38%), itraconazole in 7 (33%), and miconazole, micafungin, and fluconazole in 2 (10%). On diagnostic CT chest scans, 15 patients (71%) had cavitation, and following surgical resection, an IFI was only proven by histopathology or culture in 7 patients (33%).

The surgical data are summarized in Table 2. Pulmonary resection was performed using video-assisted thoracoscopic surgery in 11 patients (52%) and open thoracotomy in 10 (48%). The pulmonary resection procedures were partial resection in 11 cases, segmentectomy in 5, lobectomy in 4, and cavernostomy in 1. Single resection was performed in 16 patients (76%) and multiple resections in 5 (24%). The median size of the lesions was 3.5 cm (range, 0.9–8.5 cm) and 14 cases showed cavitation pathologically. The median operation time was 141 minutes (range, 62–470 minutes) and the median amount of intraoperative bleeding was 50 g (range, 0–540 g). The postoperative bacteriological diagnoses were aspergillosis in 19 cases and mucormycosis and cryptococcosis in 1 case each. The 30-day all-cause postoperative mortality rate was 0%, and fungal progression was not observed. A duodenal ulcer was noted as a postoperative complication in a single case.

Table 2. Surgical details of pulmonary resection for invasive fungal infections (N=21)

	Value
Surgical approach	
Video-assisted thoracoscopic surgery	11 (52)
Open thoracotomy	10 (48)
Surgical procedure	
Partial resection	11 (52)
Lobectomy	5 (23)
Segmentectomy	4 (19)
Cavernostomy	1 (5)
No. of lesions	
1	16
≥2	5
Median size of lesions (cm)	3.5 (0.9–8.5)
Median operation time (min)	141 (62–470)
Median amount of bleeding (g)	50 (0–540)
Postoperative pathological diagnosis	
Aspergillosis	19 (90)
Mucormycosis	1 (5)
Cryptococcosis	1 (5)
30-Day all-cause postoperative mortality	0
Recurrence of infected lesions	0
Complications	
Duodenal ulcer	1 (5)

Values are presented as number (%), number, or median (range).

The median follow-up time was 18 months (interquartile range, 2–183 months), the 1-year survival rate after surgery was 80%, and the median survival was 28 months. Five years after pulmonary resection for IFI, 9 patients (43%) had died. The 5-year overall survival rate was 49.5% (Fig. 1). The cause of death was primary malignancy in 10 patients (52%), graft-versus-host disease (GVHD) in 7 (33%), multisystem and organ failure (MSOF)/sepsis in 2 (10%), and unknown in 1 (5%).

The results of a univariate analysis of gender, age, single or multiple IFIs, tumor size, underlying malignancy, and induction for surgery are shown in Table 3. No predictor other than gender was identified.

Discussion

IFIs are common among immunocompromised patients and can be seeded at sites including the cen-

tral nervous system, liver, spleen, blood vessels, heart, eyes, gastrointestinal tract, bones, and joints, in addition to the lung [3,4]. The mortality rate of IFIs is high and infection control is difficult due to the delayed treatment of blood diseases [5]. In a recent study of IFIs that developed during chemotherapy for acute myeloid leukemia between 2004 and 2007, the 4-month survival rate of aspergilloma was 27% [6].

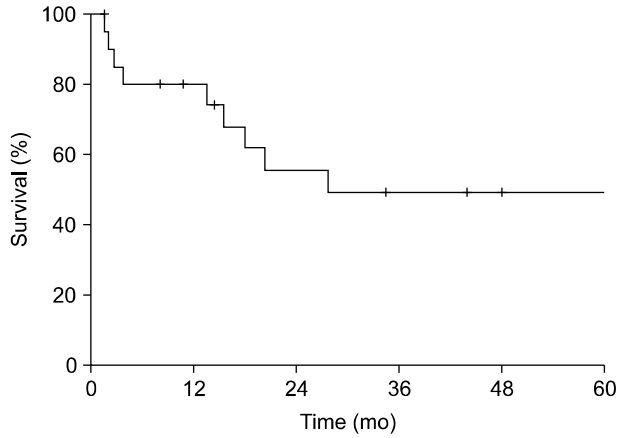

Fig. 1. Overall survival curves of patients undergoing pulmonary resection for IFI. Overall survival was examined from surgery for IFI to death or loss to follow-up. IFI, invasive fungal infection.

A definitive diagnosis of IFI is difficult despite CT findings and halo or crescent signs [7]. Diagnostic modalities such as bronchoscopy (30%–50% sensitivity) and fungal antigens in serum (20%–40% sensitivity) are useful, but limited [8,9]. In our experience, the sensitivities of bronchoscopy and fungal antigens in serum were both 33%. Nebiker et al. [10] reported a similar negative pathology rate of 27% (n=19) in a larger cohort of 71 immunocompromised patients. However, the persistence of a lesion on imaging after medical treatment led to surgical resection prior to immunosuppressant systemic therapy. In the absence of better preoperative diagnostic tools, there is currently no strategy to prevent these patients from undergoing surgical resection. Therefore, our indication for surgery for a pulmonary fungal infection is resistance to antifungal therapy and the necessity of surgical treatment before HSCT.

Pulmonary fungal infections, including pulmonary aspergillosis, are often resistant to medical treatment [11]. Pulmonary IFIs complicating hematological malignancies are associated with a high mortality rate, and the outcomes of surgical resection are not

Table 3. Prognostic factors associated with overall survival by univariate analysis

Factor	No. of patients	5-Year survival (%)	Univariate analysis	
			Hazard ratio (95% confidence interval)	p-value
Gender				
Male	13	64.2	4.17 (1.14–14.29)	0.03
Female	8	20.8		
Age (yr)				
<46	10	40	0.73 (0.22–2.39)	0.6
≥46	11	60		
No. of lesions				
1	16	37.2	0.19 (0.02–1.55)	0.122
≥2	5	80		
Tumor size (mm)				
<36	10	51.4	1.32 (0.40–4.39)	0.647
≥36	11	46.7		
Underlying malignancy				
Other than acute myeloid lymphoma	11	61.4	2.35 (0.70–7.92)	0.167
Acute myeloid lymphoma	10	31.1		
Objective of surgery				
Resistance to antifungal therapy	13	32.8	0.30 (0.06–1.47)	0.136
Necessity of surgical treatment before hematopoietic stem cell transplantation	8	72.9		

favorable. Moreover, little information is available on the long-term prognosis of patients with hematological malignancies who undergo pulmonary resection for IFI. In this retrospective study, we collected data from 21 patients with various hematological malignancies who were treated with antifungal therapy for possible, probable, or proven IFI. Only 1 patient in our series had major postoperative complications, and the overall 30-day surgical mortality rate was 0%. The only major postoperative complication was a duodenal ulcer caused by postoperative fasting for a few days. This is a better prognosis than has been reported in other studies because of the selection bias associated with lung resection for malignancy [2,10,12]. The 5-year overall survival rate was only 49.5%. The most common cause of death was malignancy. A previous study reported that the median survival was better in patients treated after 2000 than in those treated during or before 2000 (5 months versus 24 months, p=0.046) [2]. A number of factors may have contributed to this relatively good prognosis in terms of mortality, including advances in more effective antifungal therapy, more sensitive imaging modalities, improved critical care management of sepsis and MSOF, more effective systemic treatment of malignancies, and the earlier recognition and treatment of GVHD. In addition, decades of experience have improved the patient selection for surgical resection, which may have also contributed to improved survival.

The choice between surgical management and antifungal treatment depends on the extent of pulmonary lesions and the general condition of the patient. If the lesions are localized, surgery may be a preferable option to medical treatment [2]. It currently remains unclear whether surgical or medical treatment for localized lesions is better, and a prospective randomized study has not yet been conducted to compare the medical and surgical treatment of IFI in the lung. Our results showed that resection contributed to the control of local infections with an acceptable postoperative complication rate, which is consistent with previous findings [1,2].

We were unable to identify significant predictors of outcomes among patients in this cohort other than gender. The reason for this may be that the observation period of the male patients was short, affecting the survival period. No prognostic factor other than gender could be determined. This may be explained by the good prognoses in almost all cases; because the patients' primary diseases were well controlled, their lesions could be completely resected, and their tolerance of treatment was good. The most common reason for the resection of pulmonary IFI was resistance to medical management, followed by the presence of probable or proven IFI before HSCT. The Infectious Disease Society of America, which has published guidelines for the treatment of IFIs, recommended surgical evaluations for fungal lesions invading large vessels, the pericardium, or chest wall and solitary lesions detected in a work-up for HSCT [13]. No specific criteria have been established for resistance to medical management; however, we consider persistent or progressive disease in clinical or radiographic examinations after a therapeutic course of antifungal therapy to be sufficient to prompt surgical resection.

This study had several limitations. First, selection bias in the decision to perform surgery may have been present. In addition, advanced or complicated cases were excluded from surgery. These selection criteria favored better surgical outcomes by eliminating patients with a poor expected prognosis. If all patients had undergone surgery, the outcomes may have been worse than those reported with only medical therapy. Furthermore, we did not compare our cases with patients who developed IFI but did not undergo surgical resection. Doing so could have provided context for the indications for surgery and allowed us to compare the duration of antifungal treatment in both groups, as well as long-term outcomes. Another limitation of this study was the small size and heterogeneity of the patient sample, which greatly limited our ability to analyze predictors of survival.

Despite these limitations, IFI associated with hematologic malignancy is relatively rarely resected, and only a few cases have been reported to date; as such, a multicenter prospective study with the aim of improving the prognosis of patients and further refining the surgical indications is warranted.

The surgical outcomes and prognostic factors of resected pulmonary fungal infections complicating hematological malignancies were analyzed in this study. Pulmonary fungal infections in patients with hematological malignancies are often resistant to

medical treatment, and surgical treatment may be the best choice. Therefore, surgical treatment should be considered when possible.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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