Pulmonary aspergilloma: Analysis of prognosis in relation to symptoms and treatment

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Background: This study was conducted to assess the risk of surgical treatment and to evaluate surgical resection in patients with pulmonary aspergilloma.

Method: We reviewed 240 patients with pulmonary aspergilloma who were diagnosed between 1990 and 2006. Of these, 135 patients underwent surgical procedure (group A) and 105 patients were managed with conservative treatment (group B).

Result: Forty complications (29.6%) and 6 operative mortalities (4.4%) developed in group A. During the follow-up period, there were 5 recurrences (3.9%) after surgical procedure. The overall 10-year survival rates of group A and group B were 84.8% and 56.7% ($P < .001$). In multivariate analysis, age, sex, and surgical treatment were favorable prognostic factors. Symptoms of hemoptysis and blood-tinged sputum were not significant prognostic factor even in univariate analysis.

Conclusion: Our results indicate that (1) early morbidity and mortality rates of surgical treatment for pulmonary aspergilloma are acceptable, and (2) surgical treatment is helpful not only to reduce symptoms but also to prolong the survival of patients with pulmonary aspergilloma. Although more studies are needed, our data support the conclusion that surgical resection should be considered for all patients with pulmonary aspergilloma who have acceptable pulmonary reserve.

Pulmonary aspergilloma generally forms from saprophytic colonization of preexisting pulmonary cavities of *Aspergillus fumigatus*, the most common saprophytic species of *Aspergillus* in human disease, producing a fungus ball or a mycetoma.^{1,2} Massive or repetitive hemoptysis from the intrapulmonary lesion is life-threatening,³ and antifungal agents do not completely eradicate the fungus ball established in the pulmonary cavities.⁴ Surgical resection of the localized pulmonary lesion contributes not only to reducing symptoms but also to the likelihood of a permanent cure for aspergilloma.^{3,5,6} Although recent advances in thoracic surgery have indicated favorable acute and long-term outcomes⁷⁻¹⁰ compared with early high morbidity and high mortality rates^{5,11-14} with the management of pulmonary aspergilloma, there is at present no consensus about the role of surgical resection in the treatment of pulmonary aspergilloma.

This study focuses on the clinical outcome of patients with pulmonary aspergilloma. Our primary objectives were to assess the risk of surgical treatment and to evaluate the surgical resection in the treatment of pulmonary aspergilloma.

METHODS

Patients and Methods

We reviewed the records of patients with pulmonary aspergilloma who were diagnosed at our institution between January 1990 and December 2006. During this period, 240 patients were diagnosed with pulmonary aspergilloma. Of these, 135 patients underwent surgical procedure (group A). The patients were evaluated for clinical variables and were compared with 105 patients who were managed with nonsurgical treatment (group B) during the same period. Patients with invasive aspergillosis or allergic bronchopulmonary aspergillosis were excluded from this study. Diagnosis of aspergilloma was made on the basis of clinical symptoms and radiologic findings, such as tomography or computed tomographic scans. Fiberoptic bronchoscopy was performed to identify the bleeding focus. Percutaneous needle aspiration biopsy was performed when malignancy was suspected. We selected patients for surgery if they exhibited symptoms or presented with undetermined mass lesions. We routinely prescribed an oral antifungal agent (itraconazole) to be administered for 3 months following surgical resection of pulmonary aspergilloma. After the late 1990s, we preferred surgical procedure for symptomatic and asymptomatic pulmonary aspergilloma because favorable surgical series⁷⁻¹⁰ had been reported. In cases with poor pulmonary reserve or a high risk of undergoing a thoracotomy, we recommended conservative treatment such as bed rest, bronchial artery embolization, and antitussive medication. The types of aspergilloma were classified retrospectively according to the classification of Belcher and Plummer⁵: aspergilloma was considered the simple type when it developed in isolated thin-walled cysts lined by ciliated epithelium and the surrounding lung was normal; it was considered the complex type when the lesion developed in cavities formed by gross disease in the surrounding lung tissue. Follow-up data were obtained from the outpatient clinic chart reviews or by telephone calls to patients or families.

The Institutional Review Board of Yonsei University College of Medicine approved this retrospective study. The need for a subsequent individual consent of patients whose records were evaluated was waived because the individuals were not identified within the study.

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Statistical Analysis

The association between variables was analyzed by either the chi-square or *t* test. The operative mortality was defined as in-hospital mortality or mortality before postoperative day 30. Deaths owing to all causes including operative mortality were included in the survival statistics. The survival was calculated from the date of operation in group A and 12 months after diagnosis (one-half the interval of majority [90%] in group A had their operation after diagnosis) in group B. Patients (*n* = 13) who died or who had less than 12 months' follow-up after diagnosis in group B were dropped in the survival analysis. All patients were followed until either the date of death or the last follow-up (Aug 31, 2007).

The covariates in the univariate model included age, sex, pulmonary function, aspergilloma type, symptom, underlying lung disease, and treatment. The differences in survival among groups were examined using a log-rank test, and multivariate analyses were performed by means of the Cox proportional hazard model in variables that had *P* values less than .05 by univariate analyses. In a subgroup analysis, a propensity-matched analysis was used to adjust for selection bias between group A and group B. The propensity score was calculated for each patient on the basis of a logistic regression analysis of the predicted probability. Age, sex, aspergilloma type, and pulmonary function test were used as candidate variables in this propensity model. The significant predictors of treatment type were used to match each patient in the group A to a patient in the group B with the same set of predictors. A total of 114 (57 in group A and 57 in group B) of 240 patients were matched. The data were analyzed using SPSS for Windows (Statistical Package for Social Science, SPSS Inc. Chicago, Ill).

RESULTS

Demographic Characteristics

The patients included 136 men and 104 women with a median age of 51 years (range, 12–80). Clinical characteristics of patients in group A and B are compared in Table 1. Patients in group A were younger and had better pulmonary function than patients in group B. There were no significant differences in sex, underlying lung disease, and type of aspergilloma. Tuberculosis was the most common underlying lung disease. The main signs and symptoms were hemoptysis and blood-tinged sputum, and the right upper lobe and left upper lobe were the main locations. Median size of resected aspergilloma was 4.0 cm (range, 1.0–10.0).

Treatment of Pulmonary Aspergilloma

Bronchial artery embolization was attempted in 35 patients due to repeated or massive hemoptysis. Of these, 19 patients underwent surgical procedure and 16 patients were observed with medical treatment. Ultimately, 135 patients underwent surgical procedure (group A). The surgical procedures were lobectomy in 85 patients (60.8%), pneumonectomy in 21 patients (15.6%), segmentectomy in 19 patients (14.1%), wedge resections in 12 patients (8.9%), and cavernostomy with thoracoplasty in 1 patient (0.7%) who had a previous history of lobectomy. Surgical indication was repeated hemoptysis in 73 patients (54.0%), massive hemoptysis in 12 patients (8.9%), indeterminate nodule in 36 patients (26.6%), and uncontrolled infection in 14 patients (10.4%). Uncontrolled infection included lung abscess (*n* = 3), empyema (*n* = 3), destroyed lung with recurrent infection (*n* = 5), infected bulla (*n* = 1), and

TABLE 1. Clinical characteristics of the patients

Variables	Group A (<i>n</i> = 135)	Group B (<i>n</i> = 105)	<i>P</i> value
Age, median (range)	48 (12–74)	54 (23–80)	<.001
Sex, <i>n</i> (%)			.237
Male	72 (53.3%)	64 (61.0%)	
Female	63 (46.7%)	41 (39.0%)	
Underline lung disease, <i>n</i> (%)			.339
Tuberculosis	79 (58.5%)	73 (69.5%)	
Bronchiectasis	22 (16.3%)	9 (8.6%)	
Lung abscess	7 (5.2%)	3 (2.9%)	
Empyema	4 (3.0%)	1 (1.0%)	
Carcinoma	2 (1.5%)	1 (1.0%)	
Emphysema	3 (2.2%)	1 (1.0%)	
None	18 (13.3%)	17 (16.2%)	
Type of aspergilloma, <i>n</i> (%)			.523
Simple	33 (24.4%)	22 (21.0%)	
Complex	102 (75.6%)	83 (79.0%)	
Pulmonary function*			<.001
FEV ₁ (L)	2.47 ± 0.9	1.72 ± 0.8	
FEV ₁ (%)	83.1 ± 23.0	64.9 ± 27.9	
FVC (L)	3.04 ± 0.9	2.30 ± 0.9	
FVC (%)	83.8 ± 19.9	66.4 ± 23.9	
Symptoms and sign, <i>n</i> (%)			.009
Hemoptysis	83 (61.5%)	47 (44.8%)	
Blood-tinged sputum	21 (15.6%)	12 (11.4%)	
Cough and sputum	11 (8.1%)	15 (14.3%)	
Chest pain	4 (3.0%)	3 (2.9%)	
Dyspnea	3 (2.2%)	12 (11.4%)	
None	13 (9.6)	16 (15.2%)	
Location, <i>n</i> (%)			.068
Right upper lobe	53 (39.3%)	44 (41.9%)	
Right middle lobe	1 (0.7%)	—	
Right lower lobe	21 (15.6%)	8 (7.6%)	
Left upper lobe	43 (31.9%)	33 (31.4%)	
Left lower lobe	12 (8.9%)	7 (6.7%)	
Multiple locations	5 (3.7%)	13 (12.4%)	

FEV₁, Forced expiratory volume for 1 second; FVC, forced vital capacity. *Pulmonary function tests were available in 182 patients.

tuberculosis with persistent positive sputum acid-fast bacilli (*n* = 2). The median time interval between the diagnosis and surgical procedure was 0.7 months (range, 0–85.6 months). The reasons for nonsurgical treatment of 105 patients were bilateral location in 17 patients (16.2%), low pulmonary reserve in 23 patients (21.9%), refusal by the patient or family in 13 patients (12.4%), medical observation in 20 patients (19.0%), no positive symptoms (hemoptysis or blood-tinged sputum) present in 24 patients (22.9%), and comorbidity in 8 patients (7.6%) (3 with cancer, 2 with old age, 2 with liver disease, and 1 with dilated cardiomyopathy).

Surgical Outcome

Forty patients of the 135 patients in group A had complications (29.6%): prolonged air leakage > 7 days in 13 patients, incomplete reexpansion in 7 patients, postoperative bleeding in 7 patients, bronchopleural fistulae in 4 patients,

TABLE 2. Patients profile of operative mortality

No.	Age/Sex	FEV ₁ (%)	Aspergilloma type	Procedure	Complication	Procedure for complication	Cause of death
1	46/male	2.30 (71.0)	Complex	Lobectomy	BPF and empyema	Completion pneumonectomy	Pneumonia
2	66/male	0.93 (41.2)	Complex	Pneumonectomy	Bleeding	Bleeding control	Pneumonia
3	53/female	—	Complex	Pneumonectomy	—	—	Pneumonia
4	70/male	0.88 (35.0)	Complex	Lobectomy	Bleeding	Bleeding control	Pneumonia
5	68/male	1.20 (49.9)	Complex	Lobectomy	BPF and empyema	Completion pneumonectomy	Pneumonia
6	53/male	3.50 (100.0)	Complex	Pneumonectomy	—	—	Cardiovascular

FEV₁, Forced expiratory volume for 1 second; BPF, bronchopleural fistula.

wound infection in 3 patients, empyema in 3 patients, and pneumonia in 3 patients. There were 6 cases (4.4%) of operative mortality that all occurred in the complex aspergilloma. Three of 6 operative mortalities occurred after pneumonectomy, and 2 of 6 operative mortalities occurred after the completion of pneumonectomy due to complications. Causes of death were postoperative pneumonia (n = 5) and cardiovascular event (n = 1) (Table 2). During the follow-up period, we had 5 recurrences after the surgical procedure, giving a recurrence rate of 3.9% (10-year recurrence free survival was 74.8% in group A). The recurrences developed 47, 75, 79, 101, 147 months after surgical procedure. One patient was treated by thoracoplasty and is alive and symptom-free. The others were managed with conservative treatment because of poor respiratory reserve and are still alive with intermittent hemoptysis or blood-tinged sputum.

Causes of Death

The median follow-up time was 64.2 months (range, 0.4–255.8 months). Eleven patients in group A and 41 patients in group B died during the follow-up period. The causes of death were identifiable in 9 patients for group A (respiratory failure in 5, cancer related in 3, cardiovascular in 1) and in 36 patients for group B (hemoptysis related in 12, respiratory failure in 11, cancer-related in 5, cardiovascular in 6, renal failure in 1, hepatic failure in 1). We were not able to clarify the cause of death for 2 patients in group A and for 5 patients in group B.

Overall Survival

The overall 10-year survival rate of all patients was 74.0%. The overall 10-year survival rates of group A and group B were 84.8% and 56.7% ($P < .001$), respectively (Figure 1). A univariate analysis using the variables listed in Table 3 showed that the following factors were significantly associated with a good outcome: age ≤ 51 , female sex, good pulmonary reserve (forced expiratory volume for 1 second $> 79.6\%$), simple type of aspergilloma, and surgical treatment. Hemoptysis and blood-tinged sputum were not significant prognostic factors. Using multivariate analysis, we found that the independent favorable prognostic factors were age, sex, and surgical treatment (Table 4). In a subgroup analysis with propensity score-matched group

A (n = 57) and group B (n = 57), the overall 10-year survival rates of group A and group B were 78.1% and 52.3%, respectively ($P = .036$).

DISCUSSION

This study indicated that early morbidity and mortality rates after surgical treatment are acceptable. Surgical resection of pulmonary aspergilloma contributes not only to reducing symptoms but also to the likelihood of a permanent cure for aspergilloma. Long-term survival could be predicted with surgical treatment for patients with symptomatic and asymptomatic pulmonary aspergilloma.

Aspergilloma is the most common and best-recognized form of pulmonary involvement due to *Aspergillus*. Pulmonary aspergilloma usually develops in a preexisting cavity in

The number of patients at risk and survival rate with 95% confidence interval

	0	24	48	72	96	120
Group A	135	106	86	73	63	52
	100%	93.1%	90.2%	89.1%	87.8%	84.8%
	—	(88.8–97.4)	(85.2–95.2)	(83.8–94.4)	(82.3–93.3)	(78.7–90.9)
Group B	92	67	50	34	25	16
	100%	87.4%	77.7%	68.8%	61.7%	56.7%
	—	(80.6–94.2)	(69.2–86.2)	(59.3–78.3)	(51.7–71.6)	(46.6–66.8)

FIGURE 1. Kaplan-Meier analysis of overall survival for group A and group B.

TABLE 3. Prognostic factors in pulmonary aspergilloma by univariate analysis

Variables	No. of patients	10-year survival rate (95% confidence interval)	P value
Age (y)			<.001
≤51	118	92.8 (88.1–97.4)	
>51	109	43.5 (34.2–52.8)	
Sex			<.001
Male	127	67.0 (58.8–75.2)	
Female	100	83.6 (76.3–90.9)	
FEV ₁ (%)			.023
≤79.6	90	65.7 (55.9–75.5)	
>79.6	92	83.8 (77.5–90.1)	
Treatment			<.001
Surgical	135	84.8 (79.7–89.9)	
Nonsurgical	92	56.7 (48.2–65.2)	
Type of aspergilloma			.003
Simple	53	88.8 (80.3–97.3)	
Complex	174	69.1 (62.2–75.9)	
Symptoms*			.074
Symptomatic	155	77.7 (71.2–84.3)	
Asymptomatic	72	66.4 (55.5–77.3)	
Underlying lung disease			.157
Tuberculosis	149	70.6 (63.3–77.9)	
Nontuberculosis	78	81.6 (73.0–90.2)	
Location of aspergilloma			.322
Upper lobe	164	71.0 (64.1–77.9)	
Mid or lower lobe	63	81.1 (71.4–90.8)	

FEV₁, Forced expiratory volume for 1 second. *Symptoms: hemoptysis or blood-tinged sputum.

the lung.^{1,2} Many cavitary lung diseases are complicated by aspergilloma, including tuberculosis, sarcoidosis, bronchiectasis, bronchial cysts and bullae, ankylosing spondylitis, neoplasm, and pulmonary infection^{15,16}; of these, tuberculosis is the most commonly associated condition.¹⁷ In a study of 544 patients with pulmonary cavities secondary to tuberculosis, 11% had radiologic evidence of aspergilloma.¹⁸ Tuberculosis was also the most common underlying lung disease in our series. The apical portion of the upper lobe and the superior segment of the lower lobe were the most common sites of disease in our study, which seems to reflect an association with pulmonary tuberculosis.

The most common symptom associated with aspergilloma is hemoptysis.¹ Approximately 70% of our patients had either hemoptysis or blood-tinged sputum. Bleeding usually occurs from bronchial blood vessels and may be due to local invasion of blood vessels lining the cavity, endotoxins released from the fungus, or mechanical irritation of the exposed vasculature inside the cavity by the rolling fungus ball.¹⁹ Bleeding could originate from intercostal arteries as well. Extension of the mycotic process with parenchymal destruction at the periphery of the lung invading the adjacent chest wall may lead to erosion of the intercostal arteries.²⁰ Bleeding from such large arteries is unlikely to stop sponta-

TABLE 4. Prognostic factors in pulmonary aspergilloma by multivariate analysis

Variables	Hazard ratio	95% confidence interval	P value
Age (year)	1.066	1.040–1.093	<.001
Sex (male/female)	2.077	1.020–4.230	.044
FEV ₁ (%), ≤79.6/>79.6	1.193	0.586–2.428	.627
Treatment, nonsurgical/surgical	1.992	1.021–3.884	.043
Type of aspergilloma (complex/simple)	2.349	0.775–7.125	.131

Age was analyzed as a continuous variable. FEV₁, Forced expiratory volume for 1 second.

neously and could be fatal. The mortality rate from hemoptysis related to aspergilloma ranges between 2% and 14%.^{3,21,22} Twelve patients (11.4%) of 105 from group B died from a hemoptysis-related mechanism during the follow-up period in our series. The majority of cases of pulmonary aspergilloma remain stable and in 10% of cases, the aspergilloma may decrease in size or resolve spontaneously without treatment.²³ Neither the size, the complexity of the lesion, the presence of warning minor hemoptysis, nor the type of underlying disease can predict those patients who will progress to life-threatening hemoptysis.³ This threat from pulmonary aspergilloma may be one of the primary reasons for treatment.

There is no consensus on the treatment of aspergilloma. Treatment is considered only when patients become symptomatic, usually with hemoptysis. Inhaled, intracavitary, and endobronchial instillations of antifungal agents have been tried and reported in small numbers of patients, without consistent success.^{3,24,25} The role of intravenously administered amphotericin B is uncertain, and some small studies failed to show a benefit.⁴ Oral itraconazole therapy has been tried with variable results.^{26,27} Bronchial artery embolization is considered as a temporary measure in patients with life-threatening hemoptysis, as hemoptysis usually recurs due to the presence of massive collateral blood vessels.²⁸

In the absence of effective medical treatment, surgery has been regarded as the treatment of choice in operable patients with symptoms, because it removes the source of bleeding. Surgery usually offers 3 potential benefits: control of symptoms, prevention of recurrent hemoptysis, and possible prolongation of life. Patient selection for surgery depends on the balance between the risk of disease and the risk of surgery. Previous series reported mortality rates of up to 43% and morbidity including hemorrhage, residual pleural space, bronchopleural fistula, and empyema at rates of up to 60%.^{5,11–14} The fluctuating nature of the disease process and the modest surgical results restricted surgery to patients with significant symptoms. However, recent reports from the early 2000s showed a dramatic reduction in surgical-related mortality and morbidity.^{7–10} Reported mortality rates range from 0 to 4%. Akbari and colleagues⁹ reported surgical

treatment of 60 patients with aspergilloma. Their study showed 3.3% operative mortality and 33.3% morbidity with the majority of deaths and complications occurring in patients with complex aspergilloma. Park and associates⁷ reported 0.9% operative mortality and 23.6% morbidity when treating 110 patients with aspergilloma. Even though post-operative morbidity was up to 23.6% in recent series, troublesome complications were in the acceptable range, and the majority was managed without difficulty. In our series, we experienced 4.4% mortality and 29.6% morbidity with 135 patients.

In a comparison study between medical and surgical therapy, Jewkes and coworkers³ found a similar 5-year survival between the medical (65%) and surgical (75%) options in patients with minor or no hemoptysis. However, for patients with recurrent hemoptysis or a single major bleeding, the 5-year survival was 41% for medical and 84% for surgical groups, suggesting the necessity for surgical therapy for this group of patients. In our series, the overall 10-year survival of group A (84.8%) was significantly better than the survival of group B (56.7%). In multivariate analysis, surgical treatment was a significantly favorable prognostic factor. This result implies that surgical treatment offers the possibility of a survival benefit in patients with pulmonary aspergilloma. For patients without symptoms, surgical resection has not been considered. In our series, the presence of symptoms was not a significant prognostic factor in patients with aspergilloma. For patients without symptoms, the overall 10-year survival rates of patients with surgical procedure ($n = 31$) was better than that of patients with nonsurgical treatment ($n = 41$; 82.5% vs 50.5%, $P = .011$). When we select the treatment modality for patients, we should consider the risk and the benefit of the treatment. Recent advances in thoracic surgery have decreased the risk of surgery, as we have noted; the mortality rate of reports after the early 2000s were from 0% to 4% compared with up to 43% of previous series, meaning that the axis of balance for the decision could be moved toward the surgical treatment because the weight of the risk is decreased. When we consider the risk of hemoptysis-related mortality from aspergilloma and the benefit of permanent cure from surgical treatment, surgical resection could be considered for patients who have no symptoms and a tolerable pulmonary reserve with acceptable risk (4.4% mortality in all patients, 0% mortality in simple aspergilloma). The results from our series are consistent with recent trends regarding surgical management of both symptomatic and asymptomatic aspergilloma with respect to mortality and morbidity. We thought this study could be helpful to select treatment modality for pulmonary aspergilloma in a recent advanced era.

Our study has some limitations. First, those patients for surgical treatment were selected among the patients with aspergilloma, and the nature of this study was retrospectively designed. We attempted to overcome this limitation by using

a multivariate analysis and propensity score-matched subgroup analysis. Using multivariate analysis, we found that surgical treatment was a favorable factor. In a subgroup analysis with the propensity score-matched group, the patients with surgical treatment had better overall 10-year survival rates. We thought that a better comparison would be achieved by multivariate analysis in propensity score-matched subgroups, but our number of patients after matching was relatively too small to achieve significance (data was not shown). Only multicenter data collection could yield significance because our number of patients was relatively large and there were no comparison reports with large number of patients in the recent era. Second, treatment options were not homogenous during the study period. Surgical options were decided upon by surgeons and physicians without standard consensus because of the retrospective nature of this study and the lack of a worldwide standard consensus for the treatment of pulmonary aspergilloma. Further discussion with a larger population is necessary.

In summary, our results indicate that (1) early morbidity and mortality rates of surgical treatment for pulmonary aspergilloma are acceptable, (2) surgical treatment is helpful not only to reduce symptoms but also to prolong the survival of patients with pulmonary aspergilloma. Although more studies are needed, our data support the conclusion that surgical resection should be considered for patients with both symptomatic and asymptomatic pulmonary aspergilloma who have an acceptable pulmonary reserve.

All the work was performed at the Yonsei University College of Medicine, Seoul, South Korea. The authors do not have actual or potential conflict of interest.

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