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Research Article

Surgery of pulmonary aspergillomas in immunocompromised patients

Chirurgie des pulmonalen Aspergilloms bei immunsupprimierten Patienten

Abstract

Introduction: Pulmonary aspergillosis is a devastating complication in immunocompromised patients. Timing of surgery is controversial and depends on the patients' general condition.
Methods: From 2000 to 2007, 16 patients (mean age 47 years, range 20–64) underwent surgery for pulmonary aspergillosis. All patients were receiving immunosuppressive drugs due to chemotherapy of hematological malignancies, ten with additional bone marrow or stem cell transplantation. Perioperatively, aspergillosis was treated with antifungal agents. If granulocyte numbers in the peripheral blood was below $1.0x10^9$/l, granulocyte stimulating factor and granulocyte transfusions were administered perioperatively.
Results: Four patients underwent lobectomy and wedge resections of the same lung, one patient bilobectomy, two patients lobectomy, eight patients wedge resections of one lung, and one patient wedge resections of both lungs. All patients survived surgery without major complications. Five patients were bone marrow or stem cell transplanted 1, 2, 3, 7 and 10 months after surgery. Three of them died due to recurrence of the underlying malignancy. All other patients are alive and free of fungal disease.
Conclusions: Timing of surgery in the context of antifungal therapy and adequate numbers of granulocytes and platelets in the peripheral blood appear essential for successful surgical therapy and avoidance of major complications.

Keywords: thoracic surgery, pulmonary aspergillosis, immunosuppression, bone marrow transplantation, hematological malignancies

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Zusammenfassung

Hintergrund: Bei immunsupprimierten Patienten stellt die Lungenaspergillose eine schwere Komplikation dar. Der richtige Zeitpunkt der operativen Therapie wird nach wie vor kontrovers diskutiert und hängt im Wesentlichen vom Allgemeinzustand des Patienten ab.
Methoden: Zwischen 2000 und 2007 wurden 16 Patienten (Alter zwischen 20–64 Jahren, mittleres Alter 47 Jahre) aufgrund einer pulmonalen Aspergillose einer operativen Therapie zugeführt. Alle Patienten erhielten infolge einer hämato-onkologischen Grunderkrankung eine Chemotherapie oder eine immunsuppressive Therapie. Zehn Patienten hatten bereits eine Knochenmark- bzw. eine Stammzelltransplantation. Perioperativ wurde die antimykotische Therapie ununterbrochen fortgeführt. Bei einer Granulozytenzahl unter $1,0x10^9$/l im peripheren Blut wurden perioperativ Granulozyten-stimulierender Faktor und Granulozyten substituiert.
Ergebnisse: Bei vier Patienten wurde eine Lobektomie mit zusätzlicher Keilresektion in einem ipsilateralen Lungenlappen durchgeführt. Bei einem Patienten erfolgte eine Bilobektomie, bei zwei Patienten eine

Lobektomie, bei acht Patienten unilaterale Keilresektionen und bei einem weiteren Patienten Keilresektionen bilateral. Alle Patienten überstanden die operative Therapie ohne große Komplikationen.
Schlussfolgerung: Der richtige Zeitpunkt der chirurgischen Therapie im Einklang mit der antimykotischen Therapie und ausreichender Granulozyten- und Thrombozytenzahl im peripheren Blut ist für eine erfolgreiche chirurgische Therapie und zur Vermeidung von schweren Komplikationen essentiell.

Schlüsselwörter: Thoraxchirurgie, Pulmonale Aspergillose, Immunsuppression, hämatologische Malignome, Knochenmarkstransplantation

Introduction

Aspergillus is a saprophytic ubiquitous environmental fungus, which is normally found in soil, decaying vegetation and dust. There are more than 1000 species of Aspergillus organisms. However, only Aspergillus niger, fumigatus and flavus are pathogenic [1]. In general, pulmonary aspergillosis is classified as allergic, invasive and/or saprophytic infection. Invasive pulmonary aspergillosis is a severe and life-threatening disease which is observed in immunocompromised patients, while allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to Aspergillus antigens that mainly affects patients with asthma [2], [3].
In immunocompromised patients aspergillus species may grow invasively or colonize preexisting lung cavities and produce a fungus ball or an aspergilloma [4] (Figure 1).

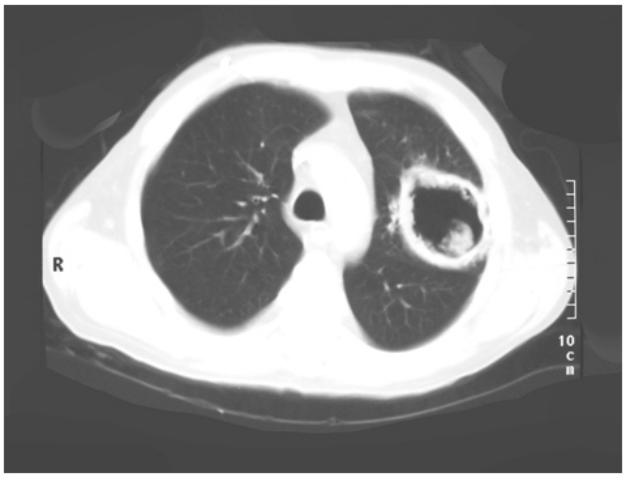

Figure 1: Computed tomogram of the chest: Aspergilloma within a cavern and thickend surrounding wall of the left lung. Surgery consisted of thoracotomy and lobectomy.

The clinical and morphological manifestation of a pathologic aspergillus infection mainly depends on lung structure with preexisting caverns and the host immune response [5]. Untreated, it may cause life-threatening complications after immunosuppression, especially in patients with underlying hematological malignancies [6]. Although new prospective screening methods for early diagnosis have been developed in recent years, invasive aspergillosis remains a challenging problem in immunocompromised patients [7], [8], [9], [10]. Over the last few years, promising antifungal therapy regimens were established [11], [12], [13], [14], [15]. However, surgery may still be necessary for the elimination of the fungus reservoir before bone marrow transplantation or because of a lack of pharmacological fungus control in immunocompromised patients. Particularly, the timing of surgery is controversial due to the high incidence of perioperative mortality and morbidity, depending on the patients' general condition [16], [17], [18], [19].

Design and methods

Sixteen patients underwent surgical therapy for pulmonary aspergillosis between September 2000 and April 2007. Two female and fourteen male patients with a mean age of 47 years (range 20 to 64 years), were referred from the Department of Hematology and Oncology and admitted to the Department of Thoracic, Cardiac and Vascular Surgery. All patients had formation of caverns due to necrotizing pulmonary aspergillosis. All patients were receiving immunosuppressive drugs for chemotherapy of a hematological malignancy; nine with acute leukemia (seven with acute myelocytic leukemia, one with B- and one with T-acute lymphatic leukemia), three with a B-chronic lymphatic leukemia, two with M. Hodgkin, one with a myelodysplastic syndrome and one with chronic myelocytic leukemia. Three of the patients had already received allogenic bone marrow transplantation and two other patients stem cell transplantation (Table 1). The diagnosis of aspergillus infection was initially suspected in all patients by chest X-rays and computed tomography. It was confirmed by cultures from bronchial lavage and PCR-investigations, respectively. Preoperatively, seven patients had moderate hemoptysis, however, no patient required an acute intervention such as bronchoscopy or surgery and no blood transfusion was needed. Cough, fever and other nonspecific signs of infection were observed in eleven patients, with five patients being asymptomatic. All patients received antifungal chemotherapy perioperatively, seven with liposomal amphotericin B; one patient liposomal amphotericin B additionally with itraconazole and three patients were treated with liposomal amphotericin B and caspofungin, one patient with caspofungin and four patients with voriconazole. Conven-

Table 1: Summary of patients' data. Time course of underlying disease, aspergillosis and bone marrow transplantation (BMT) or stem cell transplantation (SCT). m: male, f: female. MDS: myelodysplastic syndrome, CLL: chronic lymphatic leukemia, CML: chronic myelocytic leukemia, ALL: acute lymphatic leukemia, AML: acute myelocytic leukemia.

Patient No.	Age	Sex	First diagnosis of underlying disease	First diagnosis of aspergillosis	Allogeneic BMT or SCT	
					Preoperative (months)	Postoperative (months)
1	54	m	MDS 07/99	05/00	4 (BMT)	
2	46	m	B-CLL 12/96	09/99	17 (SCT)	
3	44	f	B-CLL 03/98	11/00		2 (BMT)
4	42	m	T-ALL 09/00	11/00		10 (SCT)
5	20	f	CML 03/98	06/00	18 (BMT)	
6	46	m	AML 08/01	11/01	no	
7	55	m	AML 07/01	08/01	no	
8	33	m	B-ALL 02/02	04/02		3 (SCT)
9	40	m	AML 06/01	01/02	13 (BMT)	
10	39	m	AML 09/04	09/04		7 (SCT)
11	59	m	B-CLL 06/98	12/04	no	
12	64	m	AML 01/05	05/05	no	
13	58	m	AML 11/05	12/05	no	
14	42	m	M. Hodgkin 11/06	12/06	no	
15	53	m	M. Hodgkin 05/94	01/07	102 (SCT)	
16	62	m	AML 01/07	02/07		1 (SCT)

tional chest X-ray and computed tomography investigations were performed in order to evaluate the antifungal therapy before surgery and the postoperative status. Every effort was made to improve the general condition of the patients preoperatively, including physical and respiratory training. In two patients, surgery was postponed for three and four weeks to improve respiratory function. Surgery was not performed when the neutrophilic counts were below $1.0x10^9$/l. In these patients, granulocyte colony stimulating factor (GCSF) was given and if this did not succeed neutrophilic granulocyte transfusions were administered perioperatively [20], [21], [22].

The aim of surgery was to remove every site of aspergillus infection. If necessary, concomitant surgery of other infected areas like the paranasal sinuses was performed. Care was taken to remove the pulmonary aspergillomas in toto and to avoid spillage of infected tissue to the pleural space. Pharmacological therapy was continued in the perioperative phase.

During the operation, all palpable tumors were resected. In all cases, surgical resection was performed to achieve local control of the infection and remove infected caverns as a potential infectious focus for systemic spreading. Surgical specimens were cultured and examined postoperatively by standard pathological techniques.

Results

Sixteen immunocompromised patients underwent seventeen operations. The mean interval from diagnosis of aspergillosis to surgery was 116 days, range 7 to 475 days (Table 2). All patients tolerated surgery well, there were no perioperative mortalities and no significant major surgery related complications, like empyema, hemorrhage or bronchial fistula. In two patients, prolonged chest tube drainage longer than 7 days was necessary. In one case, due to an air leak for eight days and in the other case, for twelve days because of a recurring pleural effusion. Two patients developed pleural effusion after removal of the chest tubes which was evacuated by percutaneous aspiration (Table 3).

The average lesion resected measured 41 mm (range 22–65 mm) in diameter. Altogether, seven patients requiered lobectomies: one patient underwent a bilobectomy, three a single lobectomy (one of them with thoracoplasty) and three patients lobectomy combined with a wedge resection of the same lung. In five patients a single wedge resection was performed while in three patients multiple wedge resections of the same lung were necessary. One patient required two wedge resections of both lungs in two different operations. In one patient who underwent lobectomy and wedge resection, a simultaneous pansinectomy was performed for associated aspergillus pansinusitis (Table 2). One patient had to undergo

Table 2: Interval between diagnosis of underlying malignancy to diagnosis of aspergillosis and until surgery. Surgical procedure and quantity of lung resection

Patient No.	Days from diagnosis of underlying disease to diagnosis aspergillosis	Days from diagnosis of aspergillosis to surgery	Surgical procedure
1	290	117	left upper lobectomy + wedge resection left lower lobe
2	989	475	two different operations: wedge resection left lower + upper lobe; wedge resection right lower + upper lobe
3	921	28	lower lobectomy. wedge resection left upper lobe + pansinectomy
4	28	28	wedge resection left upper lobe
5	817	420	wedge resection right upper lobe
6	78	42	wedge resection left upper lobe
7	31	193	right middle lobectomy
8	62	49	lower lobectomy + wedge resection right upper lobe
9	217	110	wedge resection left lower and upper lobe
10	16	23	left upper lobectomy + thoracoplasty
11	2372	115	wedge resection right upper lobe + middle lobe
12	91	11	right upper and middle lobectomy (bilobectomy)
13	43	44	wedge resection right upper and lower lobe
14	37	7	wedge resection right lower lobe
15	4625	7	left lower lobectomy
16	69	26	wedge resection left upper lobe

neurosurgery because of intracerebral aspergillosis eight months after lung surgery.

Pathohistology revealed vital fungal hyphae in the lung caverns of twelve patients. In four patients, the fungal infection could not be verified by histology, however, PCR-assays of resected tissue showed aspergillus DNA sequences.

Primary bone marrow transplantation and stem cell transplantation was carried out in five patients one, two, three, seven and ten months after pulmonary surgery, respectively. One of these patients died three months after surgery due to an early rejection of the stem cell grafts. Another patient died due to graft versus host reaction 16 months after lung surgery and 34 months after bone marrow transplantation. The third patient died due to rejection of the stem cell grafts 4 months after lung surgery and 5 months after stem cell transplantation. All other patients are still alive and have no evidence of aspergillus infection (Table 3).

The average platelet count at the time of the operation was $154x10^9$/l (range $63–275x10^9$/l). The average absolute leukocyte and neutrophil counts at the time of the operation was $7.0x10^9$/l (range $3.1–12.3x10^9$/l), and $4.8x10^9$/l (range $1.2–8.7x10^9$/l), respectively. In two cases granulocyte colony stimulating factor and in one patient granulocyte transfusions were administered perioperatively. In one patient platelets were substituded preoperatively (Table 4).

Pulmonary function tests were performed in all patients preoperatively. Six patients had a restrictive lung disease with an FVC of 3.2 to 4.1 l (56–67%), four further patients showed a combined obstruction: FEV 1: 1.8 to 2.9 l, (54–65%). Other important concomitant diseases were reactivated tuberculosis in one patient and aortic valve stenosis requiring aortic valve replacement 21 months later in another patient. Nine patients had an elevated serum creatinine level (1.3 to 1.9 mg/dl).

Discussion

Aspergillosis is a potentially fatal complication in immunocompromised patients [23], [24]. This infection has even become a major cause of mortality in patients after allogeneic stem cell transplantation [25]. Once clinically suspected, invasive aspergillosis needs antifungal therapy to be initiated immediately [26]. In recent years new screening methods of aspergillus infection and promising antifungal therapy regimens were established in many centres and published [27], [28], [29], [30]. In spite of the improvement of drug therapy for invasive aspergillosis the mortality rate still remains high, ranging from 35–75% [31], [32]. Approximately 50% of patients show an adequate response to drug therapy. Surgical therapy and its timing still remains controversial. Poor general condition of the patient, neutropenia, thrombocytopenia and

Table 3: Perioperative complications and patients' outcome. GvHD: graft versus host disease. m: male, f: female. AML: acute myelocytic leukemia

Patient No.	Perioperative complications	Outcome
1	none	alive
2	fever (≥38,5°C), pleural effusion five days after surgery	alive
3	fever (≥38,5°C), pleural effusion 56 days after surgery	death due to graft rejection 3 months after surgery
4	none	alive
5	none	death due to pulmonary GvHD 16 months after surgery
6	none	alive
7	relapse of AML six days after surgery	alive
8	none	alive
9	none	alive
10	none	death due to pulmonary GvHD 16 months after surgery
11	none	alive
12	none	alive
13	none	alive
14	none	alive
15	none	alive
16	none	death due to graft rejection 3 months after surgery

persistant malignancy usually result in high morbidity and mortality. In the literature, perioperative mortality varies between 14% and 32% [6], [17], [21], [25], [33], [34], [35]. In our experience, no perioperative death and only minor complications such as prolonged chest tube drainage were observed. Three late deaths were unrelated to aspergillosis and to surgery. All other patients are still alive and have no evidence of aspergillus infection. Complete resection of aspergilloma eliminates fungal focus and prevents relapse during further immunosuppressive therapies. Five patients underwent allogenic bone marrow transplantation or stem cell transplantation within a few months after lung surgery, respectively.

In all of our patients infection could be eliminated with combined surgical resection of aspergilloma and systemic antifungal therapy as has been previously published [17], [36], [37], [38], [39]. Perioperative complications seem to be directly correlated to the number of neutrophils in the peripheral blood. Therefore, we attribute our low incidence of complications to sufficient peripheral neutrophil counts (>1.0x10^9/l), careful surgical technique and intensive perioperative physical therapy.

In conclusion, we may emphasize that parenchyma saving lung resection of pulmonary aspergilloma is an adequate therapy with minor perioperative complications even in immunocompromized patients. These include patients receiving chemotherapy for hematological malignancies and patients after bone marrow or stem cell transplantation. The aim of surgery is to eliminate a potential source of infection under high-dose immunosuppressive therapy. In addition, granulocyte colony stimulating factor, granulocytes and thrombocytes should be substituted adequately, if necessary [17]. Antifungal therapy perioperatively appears important to prevent a relapse of aspergillosis. Multimodal and interdisciplinary treatment as shown in this group of patients, may help to reduce morbidity and mortality of pulmonary aspergillosis in immunocompromised patients.

Table 4: Preoperative blood count, antimycotic therapy perioperatively

Patient No.	Blood count preoperatively			Accompanying antimycotic therapy perioperatively
	Leukocytes ($x10^9$/l)	Platelets ($x10^9$/l)	Granulocytes ($x10^9$/l)	
1	6.8	35 73*	5.7	Liposomal amphotericin B, Itraconazole
2	6.8	135	4.0	Liposomal amphotericin B
3	1.4 5.3*	29 72*	0.22 2.8*	Liposomal amphotericin B
4	9.2	78	7.9	Liposomal amphotericin B
5	5.3	274	4.4	Liposomal amphotericin B
6	7.1	60 155*	5.7	Liposomal amphotericin B
7	5.0	63	4.2	Liposomal amphotericin B
8	3.8	149	1.4	Liposomal amphotericin B, Caspofungin
9	7.6	275	3.2	Liposomal amphotericin B, Caspofungin
10	8.8	247	5.1	Liposomal amphotericin B, Caspofungin
11	3.9	109	3.0	Voriconazole
12	8.7	184	6.7	Voriconazole
13	8.7	145	7.0	Liposomal amphotericin B
14	8.8	246	6.5	Voriconazole
15	12.3	225	8.7	Voriconazole
16	1.5 3.1*	129	0.2 1.2*	Caspofungin

* After substitution of platelets and granulocytes or G-CFS (granulocyte colony stimulating factor)

Notes

Conflicts of interest

None declared.

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