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Resection of Invasive Pulmonary Aspergillosis in Immunocompromised Patients

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Background: Immunocompromised patients are prone to develop invasive pulmonary aspergillosis (IPA). Relapse and high mortality rates are seen in those patients who receive subsequent immunotoxic therapy. Standard antifungal regimens often fail to completely eradicate IPA, which then warrants an aggressive surgical approach.

Methods: We performed a retrospective chart review of 13 immunocompromised patients who were considered to have IPA and who underwent surgery between 1988 and 1998.

Results: Twelve patients had a hematological malignancy and one patient had breast cancer. The diagnosis of IPA was based on a chest computed tomographic scan in all patients. A preoperative diagnosis of aspergillosis was made in three patients, and mucormycosis in one patient, by bronchoalveolar lavage. Before surgery, seven patients received chemotherapy, one patient underwent bone marrow transplantation, and five patients received a combination of chemotherapy and bone marrow transplantation. Symptoms included cough (54%), fever (54%), hemoptysis (30%), and shortness of breath (8%). Three patients (23%) were asymptomatic. The mean preoperative absolute neutrophil count was 4881 cells/μl. Seventeen thoracic operations were performed, i.e., 12 wedge resections, 4 lobectomies, and 1 pneumonectomy. One patient also underwent nephrectomy for invasive aspergillosis and one patient underwent craniotomy to resect an aspergillus brain mass. Surgical pathology revealed IPA in 13 (76%), invasive mucormycosis in 2 (15%), aspergilloma in 1, and diffuse alveolar hemorrhage in 1. Postoperative complications included the following: operative bleeding requiring transfusion, three patients; prolonged air leak, two patients; death because of hepatic/renal failure, one patient; and death because of overwhelming multisystem aspergillosis, one patient. Seven (54%) patients underwent further immunotoxic treatment with no aspergillosis recurrence. After a mean follow-up of 12 months, five (38%) patients are alive and seven (54%) have died without evidence of aspergillosis and/or mucormycosis.

Conclusions: Surgical resection, in combination with antifungal agents, is a safe and effective form of therapy for invasive mycoses. It prevents recurrence and allows for subsequent cytotoxic therapies.

Key Words: Invasive pulmonary aspergillosis—Surgery.

Patients with malignancy are being more frequently subjected to intensive chemotherapy and/or bone marrow transplantation (BMT). Various pulmonary infections readily develop in their resultant immunocompromised states.[1] Invasive pulmonary aspergillosis (IPA) is among the most devastating infections, leading to high morbidity and mortality rates. In a recent review of 1223 cases of invasive aspergillosis, disease confined to the lung carried a mortality rate of 86%.[2] The duration and extent of neutropenia has been shown, in numerous studies, to determine the risk of developing IPA.

The diagnosis of IPA is often made on clinical grounds and characteristic computed tomographic (CT) findings, because diagnostic yield of bronchoalveolar lavage (BAL) is poor and extremely variable, ranging from 22% to 50%.[3,4] Amphotericin B and itraconazole have been used to treat IPA. However, dismal response rates (33% to 54%) have been encountered in neutropenic patients who receive medical therapy alone.[2,5]

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TABLE 1. *Patient data*

Patient no.	Age, y	Sex	Diagnosis	Treatment	Neutropenia, days	Symptoms	BAL	ANC at operation	Procedure(s)	EBL, ml	Complications	Histology	Culture	Secondary treatment	Follow-up, mo	Outcome
1	28	M	AML	Chemo	Unknown	None	ND	3,000	Wedge	Min	Air leak	IPA	No growth	BMT	39	DWOA
2	32	M	AML	Chemo	30	Hemoptysis	+	2,770	Pneumonectomy	300	Bleeding	IPA	No growth	None	2	DWOA
3	66	M	AML	Chemo	18	Cough, fever	−	4,970	Wedge	150	Bleeding, HRF, death	IPA	*A. fumigatus*	None	0.5	DWOA
4	22	M	NHL	Chemo, BMT	14	Cough, fever	−	9,110	Lobectomy	Min	None	IPA	No growth	None	13	DWOA
5	32	F	AML	Chemo, BMT	18	None	ND	2,780	Wedge	Min	None	IPA	No growth	Chemo	2	AWOA
6	77	F	AML	Chemo	17	Fever	ND	3,180	Wedge × 2[a]	Min	None	IPA	No growth	Chemo	7	AWOA
7	71	M	ALL	Chemo	2	Cough	ND	1,590	Wedge × 2	50	None	IPA	No growth	Chemo	18	AWOA
8[b]	41	M	ALL	Chemo	7	Fever	ND	1,072	1. Wedge × 3[a]	100	None	IPA	No growth			
						Fever	ND	7,490	2. Wedge × 6	200	None	IPA	No growth	Chemo	9	DWOA
9	44	M	CML	BMT	20	Hemoptysis	+	6,700	Lobectomy	200	Air leak	IPA	*A. fumigatus*	None	7	AWOA
10	31	M	AML	Chemo	17	Cough, fever	−	11,690	Lobectomy	200	None	IPM	*Mucormycosis* (*absidia*)	Chemo, BMT	34	DWOM
11	21	M	CML	Chemo, BMT	14	Hemoptysis, cough	+[c]	2,540	1. Lobectomy	400	None	IPM	No growth			
						Hemoptysis, cough, SOB	ND	1,610	2. Wedge × 4	200	None	IPA	*A. fumigatus*	None	0.25	DWA
12	34	F	BC	Chemo, BMT	12	None	+	2,336	Wedge	800	Bleeding	FB	*A. flavus*	None	17	AWOA
13[d]	11	M	ALL	Chemo, BMT	28	Cough, fever	−	430	1. Wedge × 2	Min	None	IAH	No growth			
						Fever	ND	8,500	2. Wedge	75	None	IPA	No growth			
						Fever	ND	3,570	3. Wedge	125	None	IPA	No growth	Chemo	9.5	DWOA

BAL, bronchoalveolar lavage; ANC, absolute neutrophil count; EBL, estimated blood loss; AML, acute myelocytic leukemia; ND, not done; Min, minimal number; IPA, invasive pulmonary aspergillosis; BMT, blood marrow transplantation; DWOA, dead without aspergillus; HRF, hepatorenal failure; NHL, non–Hodgkin's lymphoma; AWOA, alive without aspergillus; ALL, acute lymphoblastic leukemia; CML, chronic myelocitic leukemia; IPM, invasive pulmonary mucormycosis; DWOM, dead without mucormycosis; SOB, shortness of breath; DWA, dead with aspergillus; BC, breast cancer; FB, fungus ball; IAH, intra-alveolar hemorrhage.

[a] Thoracoscopic.

[b] Patient also underwent nephrectomy and drainage of brain abscess, both secondary to invasive aspergillosis.

[c] Positive for mucormycosis.

[d] Patient also underwent resection of invasive aspergillus brain mass.

For those patients who demonstrate localized IPA unresponsive to medical therapy, surgery has been instituted to confirm the diagnosis, prevent lethal hemoptysis, eradicate remaining infection, and prevent recurrence during future immunotoxic treatments.

In the present study, we examine the experience of one institution in the treatment of patients with IPA. Patient demographics, presentation, diagnosis, surgical procedures, and outcome are discussed.

PATIENTS AND METHODS

Between January 1988 and January 1998, 2217 patients with malignancy, at Roswell Park Cancer Institute, underwent myeloablative treatments that induced neutropenia. Among these were 533 BMTs. Thirteen of these patients, who were suspected to have IPA, underwent lung resection and form the basis of this study (Table 1). A retrospective review of their charts was then undertaken. Age ranged from 11 to 77 years (mean, 39 years). There were 10 males and 3 females. Twelve patients had an underlying hematological malignancy, including six with acute myelocytic leukemia, three with acute lymphoblastic leukemia, two with chronic myelocytic leukemia, and one with non–Hodgkin's lymphoma. One patient had breast cancer. Before surgery, seven patients received high-dose chemotherapy, one patient underwent an allogeneic BMT, and five patients had received a combination of chemotherapy and BMT (four allogeneic and one autologous). The duration of severe neutropenia (absolute neutrophil count, <500) ranged from 2 to 30 days (mean, 16 days).

The diagnosis of IPA was based on a history of neutropenia, symptoms, characteristic CT finding ("halo" vs. "air crescent" sign), and BAL result. BAL was performed in eight patients, but in only four (50%) was the culture positive, i.e., three for *Aspergillus* and one for *Mucor*. A negative BAL did not dissuade us from initiating antifungal treatment on all such patients.

RESULTS

Symptoms included cough (54%), fever with a temperature of more than 39°C (54%), hemoptysis (30%), and shortness of breath (8%). Three patients (23%) were asymptomatic. Chest radiograph and a subsequent CT scan were used in all patients. Those patients who had suspicious findings were treated with appropriate antifungal medication (amphotericin B and/or itraconazole). BAL was performed at the discretion of the pulmonologist. Failed resolution of any localized pulmonary lesions after at least 14 days of medical treatment was an indication for resection. Neutrophil recovery was ideally sought before any surgical intervention. The absolute neutrophil count at the time of operation ranged from 430 to 11,690 cells/μl (mean, 4,881 cells/μl).

The various surgical procedures are listed in Table 1. Every attempt was made to remove all obvious sites of disease. Six procedures required multiple wedge resections. Four lobectomies were performed for large centrally located lesions not amenable to local resection. A left pneumonectomy was necessary in one patient with a large necrotic left upper lobe cavity as well as multiple lower lobe lesions. Three patients (patients 8, 11, and 13) had multiple procedures for persistent disease. The estimated blood loss ranged from minimal to 800 ml. Three patients required a postoperative transfusion of at least 1 unit of blood. Complications included prolonged air leak (>10 days) in two patients, one of whom required the insertion of an additional thoracostomy tube for a loculated pneumothorax.

One perioperative death occurred in a 66-year-old male undergoing chemotherapy for acute myelocytic leukemia. He developed hepatorenal failure and died on postoperative day 13. Postmortem examination failed to reveal aspergillus relapse. A second patient, with chronic myelocytic leukemia, who had received chemotherapy and, most recently, an allogeneic BMT, died postoperatively (day 7) from a combination of cytomegalovirus (CMV) pneumonitis and disseminated IPA. He had bilateral disease and underwent staged thoracotomies. His neutrophil count was 2450 and 1610 at the time of the surgeries and all gross disease was removed. His postoperative course was characterized by overwhelming sepsis and death on postoperative day 7. Postmortem examination revealed extensive CMV pneumonitis with diffuse alveolar hemorrhage and invasive aspergillosis in the lung, brain, heart, and thyroid gland.

Extrapulmonary invasive aspergillosis was found in two patients. Patient 8 required a left nephrectomy and drainage of an occipitoparietal brain abscess, and patient 13 underwent resection of an occipital brain lesion.

Histological examination confirmed IPA in 13 surgical specimens. Three patients exhibited invasive pulmonary mucormycosis (IPM). One patient who later developed IPA had an initial resection showing intra-alveolar hemorrhage. This may have represented sampling error, because a subsequent wedge resection from the same lobe showed IPA. An aspergillus fungus ball (no invasive organisms) was found in one patient (patient 12) who had stage IIB breast cancer with more than 10 positive lymph nodes. After BMT, she had a complicated course including acute respiratory distress and prolonged intubation. Barotrauma certainly occurred and she most

likely became colonized with aspergillus. It is likely that antifungal therapy cleared any invasive organisms and left behind a fungus ball.

Species identification occurred in only five cases, i.e., *A. fumigatus* in three, *A. flavus* in one, and Mucorales (*absidia*) in one.

After a mean follow-up of 12 months, five patients are alive and seven patients have died from progression of disease. None of these 12 patients have evidence of aspergillus recurrence. Of these, seven (64%) patients had undergone further chemotherapy and/or BMT.

DISCUSSION

Aspergillus is a ubiquitous fungus commonly found in soil or decaying organic matter. It causes a spectrum of clinical manifestations, i.e., allergic, cavitary, and invasive.[6] Patients who have undergone high-dose chemotherapy and/or BMT and are myelosuppressed are most prone to develop the invasive variety. IPA has a propensity for angioinvasion and can lead to fatal hemoptysis.[7,8] The duration and degree of neutropenia had been cited to be the most important risk factor for IPA. In a study by Gerson et al.,[9] 70% of patients who were neutropenic for at least 34 days developed invasive aspergillosis.

In our series, the diagnosis of IPA was suspected when a patient with a history of neutropenia exhibited certain symptomatology, CT findings, and BAL result.

Symptoms vary and are nonspecific. Approximately 25% to 33% of patients with IPA have no presenting symptoms.[5] Hemoptysis, the most feared symptom because it may lead to a fatal outcome, occurred in only three of our patients. It is rarely a presenting symptom.[10–12]

BAL carries a sensitivity that ranges from 22% to 69%, in diagnosing IPA in neutropenic patients, and is therefore unreliable.[3,4] Our results confirmed this observation because only 50% of BALs performed were positive for fungus.

The most reliable preoperative diagnostic tool used in our study was CT scanning. Persistent lesions that displayed certain characteristics (halo vs. air crescent sign) resistant to antifungal treatment were considered IPA until proven otherwise. Although plain radiographs may suggest fungal pneumonia, the use of CT scanning has greatly enabled earlier diagnosis of IPA. In a study by Caillot et al.,[13] the mean time to IPA diagnosis was reduced from 7 to 1.9 days, with the institution of thoracic CT scan in febrile neutropenic patients with plain radiographic findings of infiltrates. During a neutropenic phase, the halo sign on CT scanning is highly indicative of IPA. It appears as a mass-like infiltrate surrounded by a halo of low attenuation.[14] These early lesions correspond pathologically to central nodules of necrosis surrounded by a zone of angioinvasive aspergillus-induced hemorrhage.[15] The air crescent, or cavity, sign is characteristic of bone marrow recovery whereby neutrophils resorb necrotic tissue thereby leaving an air-filled space.

Once the diagnosis of IPA is entertained, medical therapy should be promptly instituted with amphotericin B (1 mg/kg/day). It is noteworthy that the optimum total dose that should be given has not been scientifically established. Itraconazole displays similar response rates and is reasonable first-line therapy if the patient is taking oral medication. For adults, the dose of itraconazole should be 100 mg three times daily for 4 days, followed by 200 mg twice daily. Patients treated for at least 14 days seem to have the best chance of responding. In 1996, Denning[2] published a review of 1223 cases, from the literature of invasive aspergillosis, in which he established the crude mortality rate and rate of response to therapy with amphotericin B. Among 84 patients treated for 1 to 13 days, only 1 survived. Among those with IPA treated for at least 14 days, the response rate was 83% (heart and renal transplant), 54% (leukemia), 33% (BMT), and 20% (liver transplantation). Response is based on both clinical (i.e., resolution of neutropenic fever) and radiological (resolution of halo and/or air crescent sign) criteria.

The marginal response rates to antifungals, combined with the aggressive nature of IPA, leads to mortality rates that approach 90% with medical therapy alone.[2] Furthermore, relapse rates during subsequent neutropenia are high despite the use of high-dose amphotericin B and may preclude the use of additional immunotoxic therapeutic options.[16] The addition of cytokines to standard antimycotic therapy may be an attractive option in an attempt to increase the number of circulating inflammatory cells. Colony-stimulating factors (i.e., granulocyte-macrophage colony-stimulating factors) have demonstrated in vitro to increase phagocytosis and damage to aspergillus hyphae.[17] Unfortunately, in a recently published multicenter study, growth factors did not seem to influence patient outcome.[18]

Over the past several years, surgery has been used to salvage those patients who have focal persistent IPA resistant to medical therapy.[10–13,19–21] Our algorithm has been as follows. If a patient with presumed IPA remains stable and tolerates at least 14 days of antifungal therapy, a "restaging" CT scan of the chest is performed. If persistent but localized disease is found, then pulmonary resection is recommended. Localized disease (unilateral or bilateral pulmonary involvement) is resected provided it could be removed, safely and completely, with pres-

ervation of adequate pulmonary function. Any sign of early patient decompensation warrants immediate surgical intervention.

Localized IPM has also been successfully treated with a combination of antifungal agents and, when appropriate, pulmonary resection. Although it is rarer than aspergillosis, mucormycosis carries a higher mortality rate. Patients with pulmonary mucormycosis have a clinical presentation similar to that of IPA, and its aggressiveness is directly related to host immunocompetence. Vascular invasion with thrombosis, ischemia, hemorrhage, and necrosis are common manifestations of pulmonary mucormycosis. When pulmonary mucormycosis is suspected, early diagnosis and aggressive treatment is imperative. Associated medical conditions should be optimized and ventilator support initiated if necessary. Diagnostic tests should be performed early to yield a diagnosis. It is important to remember that the clinical presentations of mucormycosis and aspergillosis are indistinguishable and the yield of BAL is equally limited. Once diagnosed, the patient should be treated with amphotericin B (using the same dosing schedule as for IPA). If the patient shows a rapid and sustained response, medical treatment and supportive care should be continued. If the patient fails to improve within 48 to 72 hours, is an acceptable operative risk, and has limited, resectable disease, consideration should be given to surgical resection. Pagano et al.[22] and Tedder et al.[23] have recently reported their results with this entity.

Initially described to prevent life-threatening hemoptysis, pulmonary resection has other benefits; confirmation or dismissal of the diagnosis may lead to alterations in medical management, and complete resection can rid the patient of any remaining fungal focus and prevent relapse during future therapies. Eradication of invasive fungus occurred in 92% of our patient cohort and is in accord with that found by others.[10–13,19–23] Relapse rates of IPA in most studies approach 0%.[10,19,20] Seven (58%) patients in the present study underwent further immunotoxic regimens (chemotherapy, five; BMT, one; and chemotherapy and BMT, one) with no evidence of aspergillus or mucormycosis (patient 8) recurrence.

The continued use of antifungal agents postoperatively has not been clearly established. However, our recommendation would be for continued use until neutrophil recovery, because these patients are at persistent risk of developing subsequent mycotic infections. Furthermore, we would recommend empiric use of such agents during subsequent myeloablative therapies.

The extent of resection has been subject to controversy. Our policy has been to completely remove all gross disease whether it be by wedge resection, lobectomy, or pneumonectomy. Obviously, patients must exhibit adequate pulmonary reserve. Thoracoscopic wedge resection was successfully performed in two patients and has been performed by others.[12]

Sixteen (94%) procedures were performed during neutrophil recovery (absolute neutrophil count, >500) and with minimal complications. Only three patients required blood transfusion. Eleven of 13 patients were discharged to go home. The 30-day mortality rate was 15% and comparable with that reported by others. One death was the result of hepatorenal failure directly related to chemotherapeutic drug toxicity and the other to a combination of IPA and CMV pneumonitis after allogeneic BMT. Wingard et al.[24] reported a mortality rate of 87% in patients with CMV interstitial pneumonitis after allogeneic BMT. The mortality of CMV pneumonitis in the setting of IPA must therefore be higher. CMV has been shown to be a risk factor for IPA in bone marrow and lung transplant recipients by causing host immune suppression.[25,26]

Although several studies in the recent literature addressing this topic have been published, the total number of patients reviewed remains small. Our study confirms what others have shown, in that surgery can be performed in this cohort of patients with little morbidity and mortality and it offers a significantly improved survival advantage compared with historical controls treated only medically. Our experience adds to the literature that supports pulmonary resection in a highly selected group of patients.

In conclusion, IPA and IPM occur in patients subjected to cytotoxic therapy-induced neutropenic states. Persistent fever, cough, or hemoptysis in a neutropenic patient should prompt a thorough workup of a possible causative agent. The diagnosis of IPA and IPM is often one of exclusion, because BAL is frequently negative. Chest x-ray is nonspecific for invasive fungal infection and must be followed by a high-resolution CT scan. If such a diagnosis is entertained, medical therapy with amphotericin B and/or itraconazole must be started promptly. Treatment for at least 14 days is preferable. Aggressive surgical resection of all gross disease is indicated for any localized pulmonary lesion resistant to antifungal treatment. Surgery is safe, well tolerated, and should be performed when neutrophil recovery is evident. It can eradicate infection and prevent relapse during any potential future therapies.

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