Invasive Aspergillosis

Progress in Early Diagnosis and Treatment

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Ninety-one patients with documented invasive infections due to an Aspergillus species were identified at Memorial Sloan-Kettering Cancer Center from July 1, 1971, through December 31, 1976. Of the 29 patients in whom the diagnosis was made during life, 10 had successful treatment and survived the Aspergillus infection by two to 17 months. An immunodiffusion test was useful in the early diagnosis of invasive aspergillosis, and in 11 patients in whom the diagnosis was supported by seroconversion and who underwent treatment, the survival rate was 64 percent. Cultures of respiratory secretions were not reliable because they often reflected only colonization. In one year, only 9 percent of the patients with Aspergillus species isolated from the sputum had an invasive infection. The lung was the commonest site of involvement, 91 percent of the patients having pulmonary lesions. The most frequently affected extrapulmonary organ was the brain (18.3 percent). Eight patients had nonpulmonary aspergillosis as the only manifestation of this infection. Most of the 91 patients had hematologic neoplasms as the underlying disease, and neutropenia and antibacterial therapy preceded the diagnosis of aspergillosis in the majority of cases.

Invasive aspergillosis continues to be a significant cause of death in patients with neoplastic disease [1–4]. A previous review from the Memorial Sloan-Kettering Cancer Center (MSKCC) [3], described the clinical and laboratory features of 93 patients in whom this diagnosis was established in the 90 months from January 1964 through June 1971. During the subsequent 66 months, from July 1971 through December 1976, an additional 91 patients with invasive aspergillosis have been recognized at this institution. The aim of this review was to substantiate our previous contention that "earlier diagnosis may lead to more effective therapy" [3] and to continue to test the role of serologic studies and cultures as diagnostic tools. This has resulted in specific recommendations for an approach to diagnosis and therapy. In addition, various characteristics of invasive aspergillosis, as observed in the current series, are compared with those in previous series.

MATERIALS AND METHODS

Patients with invasive aspergillosis were identified as follows. A computer-assisted search of all patient records at MSKCC from July 1, 1971, through December 31, 1976, was made. From these, patients were selected if they had (1) histologic evidence of tissue invasion by typical septate, acutely branching hyphae; (2) positive cultures for Aspergillus species from a normally sterile organ or body fluid as recorded in the Medical Microbiology Laboratory,

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TABLE I Diseases Associated with Invasive Aspergillosis

	Total	Attack Rate*	Pulmonary Alone	Extrapulmonary Alone	Pulmonary and Extrapulmonary
All patients	91		63 (69%)	8 (9%)	20 (22%)
Acute myelogenous leukemia	23 (25%)	1204	20	0	3
Non-Hodgkin's lymphoma	19 (21%)	355	11	3	5
Acute lymphocytic leukemia	14 (15%)	574	8	2	4
Chronic myelogenous leukemia	10 (11%)	980	5	2	3
Carcinoma†	8 (9%)	8	7	0	1
Hodgkin's disease	6 (7%)	138	5	0	1
Aplastic anemia‡	3 (3%)	—	1	0	2
Multiple myeloma	2 (2%)	138	2	0	0
Erythroleukemia	1 (1%)	—	1	0	0
Thymoma-agammaglobulinemia	1 (1%)	—	1	0	0
Other neoplasms§	3 (3%)	—	1	1	1
Tuberculosis	1 (1%)	—	1	0	0

* Cases per 10,000 new patients seen with the diagnosis at MSKCC.
† Includes two cervical, two ovarian, two hepatocellular (one with liver transplant), one breast, one oat cell.
‡ Two with bone marrow transplant.
§ Includes one osteogenic sarcoma, one spindle cell sarcoma, one neuroblastoma.

with appropriate clinical evidence of infection at that site on chart review; or (3) conversion of results of the Aspergillus immunodiffusion antibody test, as performed in the Special Microbiology Laboratory section of the Medical Microbiology Laboratory, from negative to positive in an appropriate clinical setting [5,6]. In addition, all protocols of autopsies performed at MSKCC in the time interval under study were reviewed, and patients with histopathologic evidence of aspergillosis were selected for inclusion in this report.

Records of patients with invasive aspergillosis were analyzed for the following features: age at time of diagnosis of aspergillosis; underlying disease; distribution of Aspergillus lesions; presence or absence of neutropenia (fewer than 1,000/mm^3 polymorphonuclear leukocytes for at least two days in the preceding two months); the presence of associated non-Aspergillus infections in the preceding two months; and systemic use of at least one broad-spectrum antibiotic for at least six days during the preceding two months [7].

TABLE II Antemortem Diagnosis of Invasive Aspergillosis (29 Patients)

	Survivors	Nonsurvivors
No. patients	10	19
Male/Female	6/4	14/5
Duration of amphotericin B therapy		
Mean (days)	29.2	25.7
Range (days)	7–81	3–92
No. treated <1 week	1*	3
No. treated >1 week	9 (90%)	15 (79%)
Total dose of amphotericin B		
Mean (mg)	717.2	647.4
Range	181-1363	41-3326
No. receiving <500 mg	4* (40%)	10 (53%)
No. receiving >500 mg	6 (60%)	8 (42%)
Means of diagnosis		
Seroconversion (with or without chest x-ray)	7 (70%)	4 (21%)
Abnormal chest x-ray	9 (90%)	18 (95%)
Positive Aspergillus culture	3 (30%)	10 (53%)

* One patient treated with pneumonectomy alone.

RESULTS

Background Data. From July 1971 through December 1976, 91 patients were found to have had invasive aspergillosis; in 62, initial diagnosis was made at postmortem examination. Of the remaining 29 patients, the diagnosis was suspected during life and confirmed with either histologic or serologic findings and chest roentgenogram, or culture and chest roentgenogram. Ten of the 29 patients with antemortem diagnosis of aspergillosis were treated successfully, surviving the Aspergillus infection by two to 17 months. The remaining 19 died, and invasive aspergillosis was found at autopsy. These 29 patients will be discussed in greater detail later in this paper.

Fifty-one (56 percent) patients were male, and 40 (44 percent) were female, ranging in age from six to 78 years, with a mean age of 40.2 years and a median age of 41 years. Seventy-eight (86 percent) had a hematologic neoplasm or aplastic anemia as the primary disease (**Table I**). Seventy-two (79 percent) were neutropenic, and 83 (92 percent) had had one or more systemically administered broad-spectrum antibiotic for at least one six-day period in the two-month interval preceding the diagnosis of aspergillosis. Two patients, one with inactive tuberculosis and the other with a sarcoma, had none of the other predisposing factors. A temperature of at least 38°C was present in every patient prior to the diagnosis. All of these data are similar to those in previous large series of patients with well documented invasive aspergillosis [2,3].

Antemortem Diagnosis of Invasive Aspergillosis. Twenty-nine (32 percent) of the 91 Aspergillus infections in this series were diagnosed during the life of the patient, and treatment with amphotericin B was instituted within 24 hours of the diagnosis. In three instances, the diagnosis was made without histologic or cultural documentation. One patient was treated with amphotericin B for invasive aspergillosis on the basis of seroconversion alone. Ten (34 percent) of these 29 patients survived the infection for two to 17 months after treatment. A comparison between the 10 patients who survived aspergillosis and the 19 who died and had invasive lesions at autopsy is shown in **Table II.** The complete record for one patient who died was not available for review. High total dose and long duration of amphotericin therapy themselves did not guarantee a favorable outcome, as one patient who died received more than twice the amount of amphotericin as the survivor who received the highest dose.

Survival of Invasive Aspergillosis. Table III summarizes data on the 10 patients who survived invasive aspergillosis, or, in the case of Patient 1, improved substantially. In three patients, lung lesions were removed surgically; seven received amphotericin B, in six of these, to a total of more than 600 mg. Serologic and roentgenographic data were the most important factors leading to the diagnosis in the group of survivors.

Serologic Findings. A preponderance of seroconversions (Table II) in the Aspergillus immunodiffusion test [5] was seen among the patients who survived (seven of 10), in contrast to those who died (four of 19). During the period of the present study, a total of 11 patients showed a seroconversion from negative to positive, and seven of them (64 percent) survived the infection.

Positive cultures of clinical material were found in three (30 percent) of the 10 patients who survived and in 10 (53 percent) of the 19 who died.

Aspergillus Species in Cultures. Sputum samples for smears and cultures were obtained from 48 patients. The other 43 either could not produce sputum or had no clinically evident indication for sputum studies (other than fever). In 16 of the 48 (33 percent) with sputum cultures, an Aspergillus species was isolated; in nine, on more than one occasion. In addition, cultures yielded the organism from pleural fluid in two patients, from bronchial washings in two, and from skin scrapings and external ear and nasal scrapings in one each.

For the period under study, the annual incidence of invasive aspergillosis was compared with the number of patients at MSKCC each year from whom at least one clinical specimen yielded an Aspergillus species. Relative peaks of documented invasive aspergillosis occurred in 1971, 1973 and 1976. However, the number of patients with culturable Aspergillus decreased steadily from 1971 to 1974, abruptly increasing in 1975 and 1976. Of 27 patients in 1975 who had at least one clinical isolate of Aspergillus, only five (19 percent) were subsequently proved to have invasive disease due to this fungus. In 1976, six (9 percent) of 69 patients with Aspergillus-positive cultures had documented invasive infection. Ten of 69 patients with positive cultures in 1976 had more than one culture of a respiratory secretion that yielded Aspergillus. Four of these 10 had documented invasive aspergillosis. The other six presumably had colonization, or had the noninvasive bronchopulmonary form of infection. Seventeen patients with leukemia or lymphoma had at least one positive antemortem culture, and only six of these had invasive aspergillosis. The others had no evidence of invasive aspergillosis after more than two months of follow-up. Among the patients without leukemia, 52 had positive cultures, and only one had invasive aspergillosis.

Distribution of Aspergillus Lesions: Roentgenographic Correlations. Table I lists the distribution of aspergillosis by presence or absence of pulmonary involvement in the 91 patients in this series. The lung was the most common site of invasion, found in 83 (91 percent) patients, and the only focus of aspergillosis in 63 (69 percent). Eighty of the 83 patients with pulmonary aspergillosis had had at least one chest roentgenogram within a week of the diagnosis. Only 48 (58 percent) had a lesion on the chest roentgenogram that corresponded to the Aspergillus infection more than one week before the aspergillosis was documented. In 22 (27 percent), roentgenography revealed development of new lesions in the pulmonary region found involved at autopsy within a week of diagnosis, and 10 (12.5 percent) had no roentgenographically demonstrable pleuropulmonary abnormality within one week of diagnosis, despite autopsy evidence of Aspergillus bronchopneumonia (seven patients), lung abscesses (two patients) and hemorrhagic infarctions (one patient).

Extrapulmonary Involvement. The brain was the commonest extrapulmonary organ involved, with 13 (18 percent) of the 71 examined postmortem showing Aspergillus abscesses or hemorrhagic infarcts. The gastrointestinal tract was invaded by Aspergillus species in five (6 percent) of 81 patients. The thyroid was involved in 2.5 percent of the 79 glands examined. In one patient, whose initial manifestation of invasive aspergillosis was very severe otitis externa, culture of the exudate yielded heavy growth of Serratia marcescens and Aspergillus species. He failed to respond to 531 mg of amphotericin B in the last 12 days of life (in addition to antibacterial drugs), and at autopsy the lungs were found to be heavily infected by Aspergillus.

Of the 28 patients with extrapulmonary aspergillosis, eight had no pulmonary Aspergillus lesion demonstrable

TABLE III Patients Surviving Invasive Aspergillosis

Patient	Age	Sex	Disease	Means of Diagnosis of Aspergillosis	Therapy (Total Dose/Duration)	Follow-Up
1	40	M	NHL	Seroconversion*; abnormal chest film; A. fumigatus in sputum	Amphotericin B (1,045 mg/ 81 days)	Disappearance of pulmonary infiltrates; died in relapse with Pseudomonas sepsis while receiving amphotericin B; a few Aspergillus-containing granulomata seen in lungs at autopsy
2	57	M	AML	Seroconversion*; abnormal chest film; lung biopsy confirmation	Amphotericin B (1,363 mg/ 32 days)	Resolution of pulmonary infiltrates; died outside hospital three weeks after cessation of amphotericin; no autopsy
3	58	F	AML	Seroconversion*; abnormal chest film; lung biopsy confirmation	Amphotericin B (966 mg/ 36 days)	Remission while being treated for aspergillosis; survived Clostridium lung abscess 1 month after amphotericin completed; died with relapse 4 months later; no autopsy
4	36	F	AML	Thoracentesis with growth of Aspergillus species from fluid; seroconversion later	Amphotericin B (876 mg/ 25 days)	Gradual clearing of pulmonary infiltrates, fever; died with relapse, with mixed bacterial and yeast pneumonia, 6 weeks after amphotericin discontinued; no sign of aspergillosis at autopsy
5	32	M	CML	Seroconversion*; abnormal chest film	Amphotericin B (236 mg/ 10 days)	Fever resolved with amphotericin as sole antimicrobial agent, having persisted despite intensive broad-spectrum antibacterial drugs; died with blastic crisis, with Pseudomonas pneumonia and sepsis, 7 weeks after amphotericin stopped; autopsy revealed no aspergillosis
6	48	F	AML	Seroconversion*; abnormal chest film	Amphotericin B (639 mg/ 28 days)	Bibasilar pulmonary infiltrates and fever completely resolved with onset of remission and treatment with amphotericin as sole antimicrobial agent; died 14 weeks after completion of amphotericin treatment with relapse, with bacterial pneumonia; no aspergillosis at autopsy
7	49	M	Tuberculosis, alcoholism	Positive serologic result without conversion; fungus ball on chest film	Pneumonectomy	Multiple Aspergillus-containing abscesses in addition to healed tuberculous lesions in resected lung specimen; known to have survived surgery several months, then lost to follow-up
8	57	M	AML, MM	A. fumigatus in transtracheal aspirate; positive serologic result without conversion; lung biopsy confirmation	Amphotericin B (713 mg/ 23 days)	Fever resolved with amphotericin B as only antimicrobial agent; chest film continued to improve after amphotericin stopped; died 9 weeks later with relapse of both neoplasms, without sign of respiratory infection; no autopsy
9	69	M	Erythroleukemia	Seroconversion*; fungus ball on chest film	Right upper & middle lobectomy; amphotericin B (436 mg/ 21 days)	No further clinical or radiographic sign of aspergillosis; remission continued 17 months after cessation of amphotericin B
10	22	F	AML	Fungus ball in RUL on chest film	Right upper lobectomy; amphotericin B (181 mg/7 days)	No further clinical or radiographic evidence of aspergillosis; remission continued 8 months after amphotericin stopped; seronegative for aspergillosis throughout course.

NOTE: NHL = Non-Hodgkin's lymphoma; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; MM = multiple myeloma.

* Seroconversions marked with asterisk are those which were initially negative, converted to positive, and reverted to negative during or after treatment for aspergillosis. Other seroconversions remained positive once they became positive.

TABLE IV Nonpulmonary Aspergillosis

Patient	Age	Sex	Disease	Neutropenia*	Serologic Results†	Organ Involvement	Remarks
11	12	M	NHL	+	N/D	Esophageal ulcers	Gram-negative rods in ulcers at postmortem
12	65	F	NHL	−	N/D	Brain	Confusion developed preterminally
13	78	F	Sarcoma	−	N/D	Cardiac septum	Nodal tachycardia and anterior myocardial infarction several days prior to death
14	29	M	CML	−	Neg.	Left renal abscess	Normal intravenous urogram 3 weeks prior to death; rare WBC, negative culture of urine three days prior to death
15	13	M	ALL	+	N/D	Brain, liver	Lesions organizing at postmortem examination
16	49	F	NHL	+	Neg.	Brain, heart, kidneys, thyroid	Extensive ophthalmic herpes zoster lesions possible portal of entry of Aspergillus
17	34	M	CML	+	Neg.	Brain	A. flavus recovered repeatedly from sputum antemortem; received 141 mg amphotericin B in the 7 days prior to death
18	10	M	ALL	+	Neg.	Sphenoid sinus, carotid artery, pituitary	Right abducens nerve palsy preterminally

NOTE: NHL = Non-Hodgkin's lymphoma; Sarcoma = Spindle cell sarcoma; CML = chronic myelogenous leukemia; ALL = acute lymphocytic leukemia.

* Fewer than 1,000/mm^3 polymorphonuclear leukocytes for at least two days within two months prior to death.

† Aspergillus immunodiffusion antibody within one week of death (N/D = test not done).

at autopsy. These eight patients are summarized in **Table IV.** In Patient 11, there was generalized clinical deterioration, and the presence of the esophageal ulcers was not suspected prior to death. The interventricular septal Aspergillus abscess found at autopsy in Patient 13 was heralded clinically by arrhythmias and electrocardiographic evidence of myocardial infarction. The cause of the cardiac problem was unsuspected during life. Patient 14 represents an unusual solitary manifestation of extrapulmonary aspergillosis, a renal parenchymal abscess. Measuring 1 × 1.5 cm, it was neither clinically nor microbiologically apparent antemortem.

Aspergillosis of the central nervous system was characterized by nonspecific clinical manifestations. These included seizures, confusion, visual difficulty and coma. Patient 12 had little other than changes in mental status to suggest central nervous system invasion. Patient 15 had lesions in both brain and liver that showed histologic evidence of granulomata. This sign of spontaneous healing was present, although he had never received an antifungal agent, and had relapse of disease at the time of his death. At autopsy, there was hemorrhagic bronchopneumonia due to Escherichia coli and Pseudomonas aeruginosa, but no Aspergillus elements were present in the lungs. Patient 16 had widespread extracerebral as well as cerebral aspergillosis at autopsy, which followed fulminant herpes zoster of the ophthalmic division of the trigeminal nerve of two weeks' duration. Although antemortem culture of cerebrospinal fluid did not yield a fungus, A. fumigatus was easily recovered from subarachnoid fluid taken at autopsy. Regarding Patient 17, it is impossible to say with certainty that pulmonary aspergillosis was not present before death, which was preceded by respiratory failure. Multiple sputum cultures yielded A. flavus, and the chest roentgenogram revealed progressive bilateral alveolar infiltrates. It is possible that the 141 mg of amphotericin B he received eradicated visible A. flavus from his lungs, although it continued to be isolated from his respiratory secretions. At autopsy, the lungs contained fibrinous pneumonitis with hemorrhagic infarction, but no Aspergillus hyphae. In Patient 18, a 10 year old boy, the clinical syndrome of cavernous sinus thrombosis developed preterminally. He received 428 mg of amphotericin B in the last three weeks of life, because of persistent fever unresponsive to conventional antibacterial agents, and because of the suspicion of zygomycosis of the paranasal sinuses. Autopsy did, indeed, reveal fungal invasion of the sphenoid sinuses, not by a Mucorales, but by Aspergillus species, which also involved the internal carotid artery and the pituitary.

Other Infections Associated with Invasive Aspergillosis. Eighty-five (93 percent) of the 91 patients in the current series had evidence of non-Aspergillus infections, either in the two months preceding the diagnosis of aspergillosis or at autopsy. P. aeruginosa and the Enterobacteriaceae led all the rest.

COMMENTS

An important finding of this series of patients with well documented invasive aspergillosis is the affirmation of the value of frequent serial serologic studies in the early diagnosis and cure of this infection. In 64 percent of the

survivors, initial diagnosis was based on seroconversion. Because of conversion to a positive test, a chest roentgenogram was made in Patient 9 (Table III) and showed an invasive fungus ball that developed, unsuspected, during induction of remission of erythroleukemia. The pulmonary lesion was surgically removed after achieving therapeutic amphotericin B blood levels and had not recurred for 17 months. A similar case has been described [8], except that bilateral pulmonary fungus balls were not removed. The patient died nearly four months later, after clotrimazole therapy, with the leukemia in remission, but also with cerebral Aspergillus abscess and persistent pulmonary fungus balls. There is no evidence that clotrimazole is adequate medical therapy, and patients treated with amphotericin B must be compared with those treated with surgery and amphotericin B. Some patients, such as Patient 10, evidently could not produce antibody demonstrable by current methods, even when the disease was in remission. Patients 14, 16, 17 and 18 (Table IV) had negative serologic tests also; however, in these patients, the disease had relapsed. Naturally, the behavior of the underlying disease is important in the long-term result of treatment of invasive aspergillosis [9]. In some cases, inability to achieve remission was associated with death from other causes, whether early or late, after aspergillosis was successfully treated. Patient 7, who did not have a malignant neoplasm, but who had abscesses from aspergillosis, also had an extended survival, to the extent that follow-up was possible. In Patients 2, 3 and 8, who were not examined postmortem, clinical and roentgenographic evidence of the Aspergillus infection had disappeared or was greatly diminished at the time of death. The high degree of success with patients who demonstrated seroconversion in our previous prospective study, in which there was a 57 percent survival [5], contrasts sharply with this overall series, in which 10 of 91 or 11 percent of the patients survived. However, when the diagnosis was made and patients were treated, the survival rate was 17 percent (three of 18) in those without seroconversion, and in those with seroconversion, it increased to 64 percent (seven of 11) (p value = 0.01). Other variables in factors influencing recovery such as severity of disease were not evident. In all patients with leukemia who recovered, disease went into remission and normal neutrophil counts developed. This strongly supports such serologic testing at regular intervals so as to establish negative baseline results and then observe conversions to positive as early as possible after they occur. This is of particular importance in light of our observation that severe invasive pulmonary aspergillosis may occur with chest roentgenographic abnormalities that appear very late or not at all. A drawback of the immunodiffusion test is that it takes three days. We are experimenting with more sensitive and rapid tests that can be titrated to supplement the highly specific immunodiffusion test [6].

Colonization by ubiquitous, ambient Aspergillus spores may be increased by antibiotic therapy [10,11]. Our data *do not* support the use of cultures of respiratory secretions to justify therapy with a drug as toxic as amphotericin B [12], a point that has been stressed by others [1]. We feel strongly that cultural data must be interpreted with caution, but should stimulate an intensive and rapid search for further evidence, such as serologic studies, to confirm the diagnosis.

Eighty-five (93 percent) of the 91 patients in the current series had evidence of non-Aspergillus infections, either in the two months preceding the diagnosis of aspergillosis or at autopsy. P. aeruginosa and the Enterobacteriaceae led a diverse list, in which Candida species appeared frequently.

Several interesting and unusual cases of nonpulmonary aspergillosis were found at autopsy, including a patient with sphenoid sinus involvement only rarely described [13]. In the noncompromised host, such involvement has been reported to respond to combined medical and surgical therapy [14]. A solitary renal abscess occurred in Patient 14. In previous descriptions of 12 patients with renal aspergillosis, all had evidence of invasion by the organism outside the kidney as well [2]. Others have described a 22 year old diabetic man with bilateral renal parenchymal aspergillosis with fungus balls due to this organism that obstructed the collecting system [15]. However, we believe Patient 14 to be the first reported on in the English literature to have solitary invasive renal aspergillosis and a malignant neoplasm.

In summary, invasive aspergillosis continues to claim the lives of many patients with suppressed host defenses, especially in patients in whom remission of a hematologic neoplasm is not promptly achieved. Colonization may cloud the interpretation of cultures that yield Aspergillus species.

Serologic evidence of recently-formed antibody against these organisms, in the appropriate clinical setting, has allowed early diagnosis and cure. In the patients treated following seroconversion, there was a 64 percent survival rate, which is a considerable improvement over our early experience [3] and supports the results of our more recent prospective series [5].

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