Invasive Aspergillosis in Patients with Solid Tumors

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Invasive aspergillosis (IA) has been reported only rarely among patients with solid tumors. In the current study, the authors retrospectively identified 13 episodes of definite or probable IA (using European Organization for Research and Treatment of Cancer criteria) occurring in patients with solid tumors who were treated between 1994–2003. Nine patients had pulmonary IA and three patients were found to have IA of the brain. Seven patients (54%) had primary or metastatic brain tumors and 6 patients (46%) received systemic steroids within 30 days prior to the diagnosis of IA. The majority of patients (69%) had a lymphocyte count $< 500/\mu L$ but only 1 patient was neutropenic within the 30 days before the diagnosis of IA was made. Nodular infiltrates and cavities were the most common radiologic findings. Seven patients (54%) responded to antifungal treatment. ***Cancer* 2004; 101:2300–2.** *© 2004 American Cancer Society.*

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Invasive aspergillosis (IA) is a common cause of death in patients with hematologic malignancies and allogeneic bone marrow transplant (BMT) recipients.[1] The classic risk groups for this devastating opportunistic mold infection include patients with hematologic malignancies, allogenic BMT or solid organ transplant recipients, and patients with the acquired immunodeficiency syndrome (AIDS) or rare immunodeficiencies.[1] In contrast, IA has been reported only rarely in patients with solid tumors, and to our knowledge no studies have been published to date focusing on that entity. To that end, we conducted the current retrospective study to identify the risk factors and other clinical characteristics associated with IA in patients with solid tumors.

MATERIALS AND METHODS

Between January 1993 and December 2003, we identified 13 patients with solid tumors who had IA based on a review of the microbiology records of The University of Texas M. D. Anderson Cancer Center. Patients with solid tumors who underwent hematopoietic stem cell transplantation were excluded. Routine methods for the isolation and speciation of *Aspergillus* species were followed. The patient's medical reports were reviewed for demographic data, risk factors, and disease management. Response to antifungal treatment and crude mortality were evaluated at 6 weeks after the diagnosis of IA. Autopsy records from 1993 and 2002 also were reviewed to describe the frequency of IA. The study was approved by the institutional review board. For categoric data, we used the Fisher exact test and the Student *t* test and the Wilcoxon rank sum test were used for numeric data. A *P* value ≤ 0.05 was considered statistically significant. All analyses were performed using the SPSS statistical computing package (Version 11.0 for Windows; SPSS Inc., Chicago, IL).

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Definitions

We modeled the definition of IA (proven or probable) according to the definition of IA in immunocompromised patients with cancer and recipients of hematopoietic stem cell transplantation as established by the European Organization for Research and Treatment of Cancer and the Mycosis Study Group of the National Institute of Allergy and Infectious Diseases.[2] In view of the unclear significance of positive respiratory cultures for saprophytic molds in cancer patients with solid tumors,[3] we excluded febrile patients with solid tumors with positive culture and/or cytology for *Aspergillus* species who had 1) isolation of a known pathogen that could explain the clinical picture (e.g., *Pseudomonas* in the sputum of a patient with pneumonia); 2) absence of radiologic findings compatible with IA such as nodules, the halo sign, and cavitation; and 3) response to antibacterials without the administration of antifungals and/or surgical treatment.

Neutropenia was defined as an absolute neutrophil count of $< 500/mm^3$ at the onset of infection. Response to antifungal treatment was defined as the resolution or major improvement of all clinical, mycologic, and radiologic manifestations of IA, whereas failure of antifungal treatment was defined as persistence or progression of the clinical signs and symptoms of IA and/or cultures positive for the same *Aspergillus* species that persisted during the therapy.

RESULTS

We identified 27 patients with positive cultures for *Aspergillus* species. Fourteen patients with respiratory cultures that were positive for *Aspergillus* species did not meet the criteria of probable IA and were excluded from further analysis. The majority of these 14 patients (8 patients or 57%) had lung carcinoma and 13 had a significant copathogen. The remaining 13 patients with solid tumors met the criteria of IA (proven in 9 patients and probable in 4 patients) and therefore were analyzed further (Table 1). Nine patients were found to have pulmonary IA and three were found to have brain IA. The mean age of the patients was 58 years (range, 20–76 years) and 11 patients (85%) were male. Seven patients (54%) had either primary or metastatic brain tumors. Primary brain tumor and sarcoma were the most common malignancies reported (in four patients and three patients, respectively). Six patients (46%) received systemic corticosteroids and 3 patients (23%) received $>$ 600 mg of prednisone equivalent within 30 days before the diagnosis of IA. Only 4 patients (31%) received cytotoxic chemotherapy and 2 patients (15%) received radiation therapy within the 30 days prior to the diagnosis of IA. The majority of these patients (9 patients or 69%) were lymphopenic but only 1 patient (8%) was neutropenic within the 30 days preceding the infection. No patient had received prior antifungal prophylaxis. *A. fumigatus* was the most frequently isolated *Aspergillus* species (7 patients or 54%), followed by *A. flavus* and *A. terreus* (4 patients and 2 patients, respectively). Of the nine patients with pulmonary IA, the most common findings on chest X-ray were nodular infiltrates, followed by cavitary lesions (five patients and three patients, respectively). Of the eight patients with pulmonary IA who underwent computed tomography (CT) of the chest, five were found to have cavity formation and two patients had nodular infiltrates. Overall, 6 of the 9 patients with pulmonary IA were found to have cavitary lung lesions by either chest X-ray or CT scan of the chest.

Twelve patients received antifungal agents, 4 underwent concomitant surgical resection of the *Aspergillus* lesion, and 1 patient underwent surgery only. Seven patients received oral itraconazole (at a dose of 400 mg/day), and amphotericin B (AMB)-based therapy was given to 4 patients (liposomal AMB in 3 patients and AMB deoxycholate plus voriconazole in 1 patient) as the initial antifungal treatment. Secondary antifungal therapy due to a lack of response to initial therapy was initiated in three of seven and one of three of the patients whose treatment was initiated

TABLE 1
Summary of Patients with Solid Tumors and Invasive Aspergillosis (n = 13)

Characteristics	Value
Mean age, (yrs) (range)	58.2 (20–76)
Male/female ratio	11/2
Proven/probable	9/4
Underlying malignancies	
Brain tumor	4 (30.8)
Sarcoma	3 (23.1)
Others[a]	6 (30.8)
Site of infection	
Pulmonary	9 (69.2)
Brain	3 (23.1)
Sinus	1 (7.7)
Gastrointestinal	1 (7.7)
Corticosteroids[b]	6 (46.2)
Median total cumulative dose, (mg) (range)[c]	695 (320–1240)
Chemotherapy[b]	4 (30.8)
Radiation therapy[b]	2 (15.4)
Neutropenia[b]	1 (7.70)
Lymphopenia[b]	9 (69.2)

Data are the number (%) of patients with that characteristic, unless otherwise indicated.
[a] Breast, lung, bladder, cervical, and gastric carcinoma and melanoma (in one patient each).
[b] Within 30 days before diagnosis of invasive aspergillosis.
[c] Prednisolone equivalent.

with itraconazole or AMB-based therapy, respectively. Among these patients who failed initial antifungal treatment, the median duration of itraconazole administration was 8 days (range, 7–20 days) and the duration of AMB-based therapy was 9 days.

The overall response rate to antifungal therapy (antifungals, surgery, or both) was 85% (11 of 13 patients). The total mortality at 6 weeks was found to be 23% (3 of 13 patients). Two of these 3 patients died of IA (attributable mortality rate of 67%). One patient had cerebellar IA that failed to respond to combined surgical and antifungal therapy (liposomal AMB) and the other patient had sinopulmonary IA that did not respond to the AMB lipid complex.

Finally, a total 588 patients with hematologic malignancies and 144 patients with solid tumors underwent autopsy at the M. D. Anderson Cancer Center between 1993–2002. One hundred two patients (17.3%) with hematologic malignancies and only 1 patient (0.69%) with a solid tumor were found to have IA ($P < 0.01$).

DISCUSSION

To our knowledge, IA has been studied only rarely in patients with solid tumors and has received little attention. In the current study, we report a series of patients with solid tumors who were diagnosed with IA, which is an infrequent occurrence, even in a large cancer center. Groll et al. [4] reported that the frequency of IA among patients in their study with solid tumors who underwent autopsy was 0.68%, a percentage that is nearly identical to that reported in the current study.

In the current study, IA was found to occur predominantly in patients having brain tumors (primary or metastatic) as their underlying malignancy who were treated with high-dose steroids. In fact, nearly half of the patients in the current study had received high doses of systemic steroids, which is a recognized risk factor for IA.[5] Steroids and lymphopenia appeared to be the dominant risk factors for IA in patients with solid tumors. Conversely, prolonged and profound neutropenia, a well known risk factor for IA in patients with underlying hematologic malignancies,[1] was reported to have occurred only once in the current study cohort, most likely because neutropenia is transient and not profound in cancer patients with solid tumors.

Using stringent criteria, we found that only one of the nine patients in the current study with lung carcinoma and positive cultures for *Aspergillus* had pulmonary IA. Characterizing the significance of a positive culture for *Aspergillus* in patients with lung carcinoma is difficult. These patients commonly have underlying structural lung disease and chronic colonization by *Aspergillus*, have fever resulting from postobstructive pneumonia, and may have lung cavitations or nodules as a result of their malignancy. We believe that unless these patients have iatrogenic hypercortisolism (e.g., due to the treatment of brain metastases), the isolation of *Aspergillus* from the respiratory secretions is of little significance.

The response of IA to antifungal treatment was found to be quite poor in the patient population in the current study, which was comprised typically of leukemia patients or those who underwent BMT, with a 6-week mortality rate of 85%.[6] In contrast, only 2 of the 13 patients (15%) in the current study with solid tumors and IA were reported to have treatment failure. Similarly, in a multiinstitutional registry of 595 unselected patients with IA, Patterson et al. reported low treatment failure rates (12%) in patients with solid tumors.[7] Based on that study and our own experience, itraconazole appears to be an acceptable therapeutic option in these patients.

IA in patients with solid tumors remains a rare infection. In the current study, a brain tumor was found to be the most common underlying condition and steroid use was the predominant predisposing factor. Response to treatment may be better in these patients compared with IA occurring in patients with hematologic malignancies.

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