Zygomycosis in the 1990s in a Tertiary-Care Cancer Center

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Twenty-four patients with cancer met predetermined criteria for a diagnosis of zygomycosis over a 10-year period at our institution. All had hematologic malignancy, and most had either neutropenia or steroid use as a risk factor. Pulmonary involvement mimicking invasive aspergillosis was the most common presentation, and dissemination was seen in 58% of patients on whom autopsies were performed. Three-fourths of the patients with pulmonary zygomycosis had pathogenic microorganisms other than zygomycetes isolated from respiratory specimens. The sensitivity of cultures in detecting zygomycetes from respiratory specimens was low. A culture positive for zygomycetes was typically a preterminal finding in the fatal, acute cases. Two-thirds of the patients died. Favorable outcome seemed to correlate with lack of pulmonary involvement, surgical debridement, neutrophil recovery, and a cumulative total amphotericin B dose of 2000 mg. Therapy with high-dose amphotericin B, combined with aggressive surgery and immune reconstitution, offers the best chance for survival of cancer patients with zygomycosis.

Zygomycosis is a rare infection caused by fungi of the order Mucorales (class Zygomycetes), with the most common causative organisms being *Mucor, Rhizopus, Absidia,* and *Rhizomucor* species [1]. The pulmonary, sinopulmonary, rhinocerebral, disseminated, gastrointestinal, cutaneous, and other rarer forms of zygomycosis have been described [1].

Studies since the 1960s have described the classic manifestations and risk factors of zygomycosis in patients with cancer [2, 3]. Zygomycosis has typically been seen in patients with leukemia who received high doses of steroids or those with prolonged, profound neutropenia [1–4]. In contrast to the rhinocerebral form of zygomycosis typically seen in patients with ketoacidosis, the pulmonary form of the disease has been more frequently encountered in patients with malignancy [1, 2]. In addition, those older studies emphasized the poor outcome of this opportunistic mycosis in the absence of immune reconstitution, despite therapy with high doses of amphotericin B (AmB) [2–5]. Late diagnosis of zygomycosis may have also contributed to the poor outcome [2, 3].

The past decade has seen the introduction of promising therapies to our antifungal armamentarium: lipid formulations of AmB and immunotherapy-based approaches, such as the use of colony-stimulating factors (CSFs) and granulocyte-CSF (G-CSF)–primed donor WBC transfusions [6]. Nevertheless, all recently published studies of zygomycosis in patients with cancer consist of case reports or reports of small case series [7–11], with the exception of a study from 1987 through 1995 that included 37 patients with leukemia in 18 different institutions in Italy who had histopathologically proven zygomycosis [12]. All the previous studies required histopathology (mostly autopsy) for the diagnosis, and thus selected patients with more severe infection and poorer prognosis.

The purpose of this study was to examine whether there have been changes in the natural history of zygomycosis in patients with cancer, on the basis of a review of our experience at the University of Texas M. D. Anderson Cancer Center (MDACC) over the past decade. We also evaluated the significance of the isolation of zygomycetes in culture specimens collected from patients with malignancy.

Methods

Cases of zygomycosis were identified by review of the histopathology and microbiology culture reports from the period 1989–1998. The histologic diagnosis of zygomycosis was established by identification of broad, twisted, branching, nonseptate, "ribbonlike" hyphae with use of periodic acid–Schiff or Grocott-Gomori methenamine silver nitrate stains. The microbiological diagnosis of zygomycetes was confirmed by means of standard methods [13]. To determine the significance of cultures positive for zygomycetes, we retrospectively reviewed the medical records of patients and obtained information about their underlying malignancy, risk factors, clinical signs and symptoms, diagnostic work up, prophylaxis, therapeutic treatment, and outcome.

We established 4 categories for the significance of a culture positive for zygomycetes: definite zygomycosis, probable zygomycosis, possible zygomycosis, and colonization by zygomycetes. We modeled the definitions of zygomycosis after the Mycoses Study Group criteria [14]. Definite zygomycosis was defined as pathological find-

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Table 1. Significance of a culture positive for zygomycetes in 42 patients with cancer.

Diagnosis	Hematologic malignancy	Solid tumor	Total
Definite zygomycosis	18	0	18
Histopathologic evidence only	6	0	6
Histopathologic evidence and positive culture	12	0	12
Probable zygomycosis	6	0	6
Possible zygomycosis	5	0	5
Colonization	3	10	13
Total no. of patients with positive culture	26	10	36
Total no. of patients	32	10	42

NOTE. Data are no. of patients.

ings consistent with a diagnosis of zygomycosis, with or without a zygomycetes-positive culture of a specimen from the same site. Probable zygomycosis was defined as the appearance of the clinical and radiographic signs of infection and at least 1 zygomycetes-positive culture of a specimen from the affected site, in the absence of histopathologic confirmation and of other pathogens that could explain the clinical picture. If the respiratory specimen was sputum, at least 2 different specimens had to be positive. Possible zygomycosis was defined as the appearance of clinical and radiographic signs of infection and 1 culture positive for zygomycetes and/or the presence of other pathogens in the same culture, in the absence of histopathologic confirmation. Finally, colonization or contamination of the culture specimen by zygomycetes was defined as a zygomycetes-positive culture of a specimen obtained from a patient with no clinical signs of infection.

Risk factors for zygomycosis were defined as the following: neutropenia (<500 neutrophils/mm^3), lymphopenia (<1000 lymphocytes/mm^3), hyperglycemia (blood glucose level >200 mg/dL for $\geq$7 days before onset of infection), preexisting renal failure (serum creatinine level >2.5 mg/dL for $\geq$14 days before onset of infection), and significant steroid use (>600-mg cumulative dose of prednisone in the 4 weeks before the onset of infection).

Because of the difficulties in the microbiological detection of molds in general [13] and zygomycetes in particular [2], the primary outcome of treatment focused on clinical response. Response to antifungal therapy was defined as the resolution or diminishment of all signs, symptoms, and radiographic changes of infection. Failure was defined as deterioration of clinical and radiographic abnormalities, and death. Zygomycosis was considered a contributory cause of death at autopsy if there was histopathologic involvement of a major organ and there was antemortem evidence of severe dysfunction of the affected organ. Categorical data were analyzed with the χ^2 or Fisher's exact test (Epi Info, version 6.04; Centers for Disease Control and Prevention, Atlanta). Significant P values were set at <.05.

Results

Of the 42 cancer patients included in this analysis, 36 had cultures positive for zygomycetes. For the remaining 6 patients the diagnosis was made by histopathologic identification alone. We found 18 cases of definite zygomycosis, 6 cases of probable zygomycosis, 5 cases of possible zygomycosis, and 13 cases of colonization by zygomycetes. Hematologic malignancy was present in all 24 patients with definite or probable zygomycosis (table 1). Eighteen (69%) of the 26 patients who had hematologic malignancy and a culture positive for zygomycetes had definite or probable zygomycosis, in contrast to none of the 10 patients who had solid tumors (P = .002; table 1).

The clinical characteristics of the 24 patients with definite or probable zygomycosis are outlined in table 2. The majority of the patients with hematologic malignancy (17 [70%] of 24) had a relapse of their malignancy at the time of diagnosis. The remaining 7 patients either were receiving induction chemotherapy (5 patients) or were in complete remission from their leukemia but had severe graft-versus-host disease following allogeneic bone marrow transplantation (2 patients). Ten patients were recipients of bone marrow transplants (allogeneic in 8 patients, syngeneic in 1, and autologous in 1).

The incidence of zygomycosis at autopsy was 0.7% (12 of 1765 autopsies performed during the study period). The incidence among patients with hematologic malignancies was 1.9% (12 of 624 autopsies). The frequency of zygomycosis appeared to increase over the study period, with 17 of the 24 cases of definite or probable zygomycosis diagnosed during the last 5 years. The incidence of zygomycosis was found to be 7 per 88,207 or 8 per 100,000 admissions during 1989–1993 versus 17 per 82,490 or 20 per 100,000 admissions during 1994–1998.

Table 2. Summary of data concerning patients with definite or probable zygomycosis at our facility during a 10-year period.

Variable	Definite (n = 18)	Probable (n = 6)	Total (n = 24)
Sex (male/female)	12/6	3/3	15/9
Underlying cancer			
Acute myelogenous leukemia	4	3	7
Myelodysplastic syndrome	4	0	4
Chronic myelocytic leukemia	3	1	4
Multiple myeloma	2	2	4
Chronic lymphocytic leukemia	3	0	3
Acute lymphocytic leukemia	2	0	2
Predisposing factor[a]			
Neutropenia	16	6	22
Steroids	16	4	20
Lymphopenia	14	6	20
Bone marrow transplantation	9	1	10
Hyperglycemia	5	1	6
Preexisting renal failure	3	1	4
Splenectomy	1	0	1
Genus of zygomycetes identified			
Mucor	6	4	10
Rhizopus	3	2	5
Cuminghamella	2	0	2
Syncephalastrum	1	0	1
None isolated	6	0	6
Time of diagnosis			
After death	12	0	12
Before death	6	6	12
Outcome of treatment			
Failure	15	2	17
Response	3	4	7

NOTE. Data are no. of patients.
[a] Most patients had multiple risk factors.

No seasonal variation or temporal or spatial clustering of cases was observed.

Almost all (96%) of the patients with definite or probable zygomycosis received immunosuppressive agents in the 4 weeks preceding the diagnosis of zygomycosis. Seventeen patients (71%) received cytotoxic chemotherapy within 4 weeks before their infection developed. Steroids were given to 20 patients (83%) in the month before onset of the infection (table 2); the mean cumulative dose of steroids per patient was 3938 mg of prednisone (median, 1187 mg). Neutropenia was noted at the onset of infection in 17 (71%) of 24 patients; the average duration of neutropenia was 16 days (range, 5–54 days). On the other hand, hyperglycemia was seen in 6 patients (25%).

Pulmonary involvement was clinically apparent in 17 (71%) of the cases of definite or probable zygomycosis and was proven by histopathology in 13 cases. Pulmonary involvement by zygomycosis was seen in all 12 autopsy-proven cases (table 3); 7 (58%) of these patients had the disseminated form of the infection. In 4 of these 7 cases involvement of the gastrointestinal tract was noted, and this was symptomatic in 3 cases. In contrast, the other sites of involvement found at autopsy in patients with disseminated disease (kidneys in 3 cases; CNS, heart, and liver in 2 cases each; and spleen and lymph nodes in 1 case each) were clinically silent. Finally, the rhinocerebral form of the disease was distinctly uncommon (1 case; table 3).

In patients with lung involvement by zygomycetes, the clinical presentation was nonspecific and included fever (21 patients) and respiratory symptoms such as dyspnea (12), pleuritic chest pain (8), cough (7), and hemoptysis (3). All 17 patients had an abnormal chest radiograph. The radiography revealed a multitude of patterns such as focal consolidation (5), cavitation (4), and widespread infiltrates (4) or nodules (3). Thirteen (76%) of the 17 patients with definite or probable pulmonary zygomycosis had a respiratory culture positive for another pathogen. Concomitant pneumonia due to mold (either *Aspergillus* or *Fusarium* species) was found in 6 (46%) of 13 patients with histopathologically proven pulmonary zygomycosis. Overall, the majority (83%) of the 24 patients with definite or probable zygomycosis had a concomitant infection. In particular, other opportunistic fungal infections were seen in one-third of these patients (due to *Aspergillus* species in 4, *Fusarium* species in 2, and *Candida* species in 2).

Mucor was the predominant genus seen in 10 (56%) of the 18 cases in which a culture was positive for zygomycetes (table 2). In contrast, *Mucor* was seen in only 2 (15%) of the 13 cases in which the culture was deemed to be positive as a result of contamination or colonization ($P = .03$). On the other hand, *Rhizopus* was seen in 7 (54%) of the 13 cases of colonization and in 5 (28%) of the 18 cases of probable or definite zygomycosis ($P = .15$). In one-third of the patients with histopathologically proven zygomycosis, the organism failed to grow in culture (table 2). Only 1 of those patients had previously received treatment with AmB.

Table 3. Sites involved in 24 cancer patients with definite or probable zygomycosis.

Site involved	Definite	Probable	Total
Pulmonary	5 (12)[a]	3	8 (15)
Sinuses	3	0	3
Sinopulmonary	1	1	2
Rhinocerebral	1	0	1
Disseminated[b]	7	0	7
Gastrointestinal tract	0	2	2
Soft tissue	1	0	1

NOTE. Data are no. of patients.

[a] Five had pulmonary involvement only; an additional 7 patients also had lung involvement and died with disseminated zygomycosis (thus the totals of 12 and 15 in parentheses in this row).

[b] Disseminated disease was found at autopsy (with lung involvement in all).

A diagnosis of zygomycosis was rarely suspected, and on the basis of the clinical presentation the diagnosis was presumed to be invasive aspergillosis for nearly all patients. The correct diagnosis was made before death in 50% of the cases (table 2). Zygomycosis was diagnosed before death for only 2 of the 12 patients with the infection on whom an autopsy was performed. In all 4 patients with sinus involvement, the sinus biopsy was diagnostic and permitted an antemortem diagnosis. However, for a majority of the patients whose infection was diagnosed before death, the time from diagnosis to death was only a few days. In 14 (88%) of the 16 patients who died within 1 month of diagnosis, zygomycosis was diagnosed either at autopsy (10 patients) or around the time of death (4).

Among the 13 patients with histopathologically proven pneumonia caused by zygomycetes, the respiratory specimens from 25% were positive for zygomycosis before death. Sputum cultures were positive for only 2 (25%) of the 8 patients with pulmonary zygomycosis whose sputum was cultured. Bronchoalveolar lavage specimens from only 3 (25%) of the 12 patients with pulmonary zygomycosis who underwent the procedure was also positive for zygomycetes. On the other hand, postmortem cultures were positive for 10 (83%) of the 12 patients with fatal pulmonary zygomycosis noted at autopsy.

Almost all (96%) of the patients with zygomycosis had received antifungal prophylaxis (fluconazole, 17 patients; itraconazole, 7; and aerosolized AmB, 4). Among the 24 patients with definite or probable zygomycosis, 20 (83%) received various combinations of antifungals (AmB, 10 patients; lipid formulations of AmB, 10; fluconazole, 5; itraconazole, 4; and 5-fluorocytosine, 2). The median daily dose of AmB was 50 mg (range, 30–110 mg); the median cumulative dose was 440 mg (range, 30–2610 mg); the median duration of treatment was 7 days (range, 1–37 days). Among the patients who received lipid formulations of AmB, the median daily dose, cumulative dose, and duration of therapy were 297 mg (range, 156–400 mg), 2810 mg (range 500–32,248 mg), and 10 days (range, 2–228 days), respectively.

AmB or one of its lipid formulations was given empirically before the definite diagnosis of zygomycosis to 10 (50%) of the

20 patients. Five patients underwent surgery (sinus debridement in 4 and debridement of a necrotic soft-tissue lesion in 1). Finally, 8 patients (33%) received granulocyte-macrophage–CSF (GM-CSF)–primed donor WBC transfusions, whereas 16 patients received CSFs alone (14 with G-CSF and 2 with GM-CSF).

Seventeen patients died within 3 months after diagnosis of zygomycosis; the infection was considered to contribute to the deaths of 11 (92%) of the 12 patients on whom an autopsy was performed. The course of zygomycosis in fatal cases was rapid. The duration of 13 (76%) of the 17 fatal cases of the disease was <4 weeks from the onset of symptoms.

Therapy was successful for 8 patients (33%). Four of the 8 patients who received only standard AmB and 4 of the 8 patients who received only lipid formulations of AmB responded to therapy. The mortality among patients who either did not receive AmB or received AmB for <1 week was 100%. The mean dose of AmB during the first week of therapy for the 4 responders who received standard AmB was 0.9 mg/kg/d (range, 0.5–1.2 mg/kg/d), and that for the 4 responders who received lipid formulations of AmB was 7 mg/kg/d (range, 5–9 mg/kg/d).

Of the responders who started with a daily dose of AmB of <1 mg/kg/d (or <5 mg/kg/d for the lipid formulations), all 4 had a rapid escalation of the daily dose of AmB (median time to achievement of maximum dose, 3 days). Of the 6 nonresponders who received AmB for >1 week, 3 received regular AmB and 3 received lipid formulations of AmB (mean doses, 0.76 mg/kg/d and 5.5 mg/kg/d, respectively), and only 1 had a rapid escalation of the daily dose of AmB. In addition, the interval (mean) from the onset of symptoms to the onset of AmB treatment for the 8 patients who responded was 6 days, vs. 9 days for patients who did not respond.

In 2 patients of the latter group, zygomycosis occurred as a breakthrough infection despite treatment with AmB lipid complex at a dosage of 5 mg/kg/d or AmB at a dosage of 0.9 mg/kg/d. A cumulative total AmB dose of 2000 mg was associated with a favorable outcome, since 6 of 11 patients who received >2 g of AmB responded, versus 0 of 9 patients who received <2 g of the drug ($P = .01$). A favorable outcome also correlated with nonpulmonary involvement (6 of 6 patients; $P = .0002$), surgical debridement (4 of 5 patients; $P = .03$), neutrophil recovery (5 of 12 patients whose neutrophil count recovered vs. 0 of 9 patients whose counts did not recover; $P = .01$). There was a trend toward better outcomes when treatment with WBC transfusions was given (4 of 8 patients; $P = \text{NS}$).

Discussion

We have presented what we believe to be the largest series of zygomycosis cases involving patients with cancer at a single institution in the 1990s. All patients had the typical immunologic defects previously associated with this infection, such as neutropenia and immune dysfunction due to systemic steroid use. Hematologic malignancies were predominant in our series, as in older reports [2]. Zygomycosis remained a relatively uncommon disease in our institution during the study period, being found at autopsy in only 1.9% of the patients dying with hematologic malignancy. Funada et al. [7] reported a similar incidence of 2.1% at autopsy among patients with acute leukemia. The low incidence of zygomycosis at autopsy contrasts with the high incidence of invasive aspergillosis at autopsy among patients with hematologic malignancy at our institution (95 of 484 autopsies, or 19.6%, for the period of 1990–1998; unpublished data).

In addition, zygomycosis complicated only 10 of the 4020 bone marrow transplants at MDACC in the period 1989–1998. Thus, the incidence of zygomycosis among bone marrow transplant recipients was also low (2.5 %) but somewhat higher than the 0.9% previously reported [15]. The incidence of zygomycosis at MDACC increased during this decade, since the incidence was only 0.6% among patients with leukemia in the period 1960–1971 [16] and 0.8% in the period 1978–1984 (unpublished data, present authors). We do not have an explanation for this increase in incidence. On the other hand, we found no case of zygomycosis among patients with solid tumors.

The rarity of zygomycosis in patients with solid tumors was recognized almost 30 years ago [2, 17]. In a series of 26 autopsy-proven cases of zygomycosis from among 4000 patients with malignancy, only 1 patient had an underlying solid tumor [2].

The presentation of zygomycosis was elusive and mimicked that of other invasive mold infections. The sinopulmonary form of the disease was the predominant presentation. The rarity of a sino-orbital presentation in patients with cancer and zygomycosis suggests that there are host-dependent differences in the pathogenesis of this infection in different patient populations [18]. It is noteworthy that one-third of the patients in our series had concomitant opportunistic fungal infections, reflecting the profound immunosuppression of the affected patients.

Our study showed that isolation of zygomycetes from patients with cancer who have no risk factors or clinically evident infection probably represents colonization. On the other hand, the pretest probability of a culture positive for zygomycetes was high for patients with leukemia, since only 12% of these patients were deemed to be only colonized by zygomycetes (table 1). *Mucor* seemed to be an uncommon cause of contamination, but *Rhizopus* was a frequent contaminant. Whether this represents differences in the virulence of various zygomycetes is unknown.

Nevertheless, the microbiological diagnosis of zygomycosis continued to have a low sensitivity over the study period. Cultures of lower respiratory specimens were negative for zygomycosis in 75% of the cases of histopathologically proven pulmonary zygomycosis. The low yield of bronchoalveolar lavage in diagnosing opportunistic mold infections, especially aspergillosis, has been reported by others [19]. In addition, the high

incidence of concomitant pulmonary infections may have contributed to the low sensitivity of the respiratory cultures for zygomycetes and thus delayed the diagnosis further. More sensitive tests such as PCR [20] are needed to diagnose the infection at an earlier stage. Early diagnosis and treatment have been shown to reduce mortality associated with the more common invasive mold infections in this patient population [21].

The present study and other recent studies [12] show that the mortality rate among cancer patients with zygomycosis continues to be high. This is in contrast to the relatively good prognosis for patients with zygomycosis who have nonmalignant underlying diseases [18]. The poor prognosis could be explained by both the inherent resistance of zygomycetes to antifungal treatment and the fact that diagnosis is still difficult and comes late. The course was frequently rapid and the diagnosis was commonly a preterminal event for the patients described in our series. Our study also confirmed that hyperacute disease and involvement of the lungs or $\geqslant 2$ noncontiguous sites confer a poor prognosis, as previously reported [11, 22, 23]. However, the low number of cases precluded multivariate analysis of independent prognostic variables.

Our study and others [1, 10, 23–25] stress the importance of the combination of early aggressive surgical excision of the necrotic lesions, restoration of immune function, and intense therapy with AmB. For patients who received a cumulative dose of >2 g of AmB the prognosis was good, whereas 100% of the patients who received no AmB or who received it for only a few days died. However, bias caused by the selection of survivors from the hyperacute form of this infection could underline such an association.

Evaluation of the reported benefit of novel therapeutic strategies such as the use of lipid formulations of AmB [23, 26–29] or CSFs with [23, 24] or without WBC transfusions [30] was hampered by the small number and heterogeneity of cases in our study. Several reports of uncontrolled studies describe successful outcomes for patients with leukemia and zygomycosis who received lipid formulations of AmB [23, 26–29]. Whether this represents publication bias toward successfully treated cases is unknown. Walsh et al. reported a successful outcome with the use of AmB lipid complex, at a dosage of 5 mg/kg/d, for 71% of 24 patients with zygomycosis [29]. The majority of those patients (75%) had a nonmalignant underlying disease.

The relatively good prognosis associated with zygomycosis in this patient population has been previously shown [18]. No advantage of using the lipid formulations of AmB emerged from our study. Our study also did not include patients who received hyperbaric oxygen, a therapeutic modality described as promising in anecdotal reports [31]. Finally, no role for antifungal prophylaxis emerged from our study, as zygomycosis commonly developed in patients receiving antifungal prophylaxis. Effective prophylaxis is critical to the successful management of these difficult-to-diagnose infections.

Despite the recent advances in diagnosis and management of opportunistic fungal infections, zygomycosis, although still infrequent, continues to pose formidable diagnostic and therapeutic challenges with regard to patients with cancer. Prompt institution of high doses of AmB (1–1.5 mg/kg/d), combined with aggressive surgery and correction of the immune deficits, if possible, offers the best hope for survival. The use of lipid formulations of AmB has the advantage of reducing nephrotoxicity and permitting the administration of higher doses, which may increase efficacy.

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