Cryptococcosis in Patients with Cancer

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Records of 31 patients with cancer who did not have known human immunodeficiency virus infection and who developed culture-proven cryptococcosis during the period of 1989–1999 (incidence of 18 cases per 100,000 admissions) were retrospectively reviewed. Several presentations of cryptococcosis were seen, including pulmonary in 19 patients (13 of which were symptomatic), disseminated in 6, meningeal in 3, and other, less common manifestations in 3. Hematologic malignancy (in 20 patients [65%]) was the most common underlying disease. Lymphopenia was present in 19 patients (61%). Previous steroid use was noted in 16 patients (51%). The diagnosis of cryptococcosis was rarely suspected; lung and brain malignancy were frequent initial impressions. Cryptococcosis was diagnosed postmortem in only 2 cases (6%). In cases of both pulmonary and meningeal cryptococcosis, the yield of invasive diagnostic procedures was good. Antifungal treatment was heterogeneous, but only 18% of patients who received it had treatment failure. Fluconazole monotherapy was successful in 92% of patients. In conclusion, cryptococcosis is rare in patients with cancer and appears to have a relatively good diagnostic yield and therapeutic outcome.

Cryptococcosis, caused by the yeast Cryptococcus neoformans, is an uncommon invasive fungal infection in patients with malignancy [1–3]. Meningeal, pulmonary, disseminated, cutaneous, cryptococcemic, and other, rarer forms of cryptococcosis have been described in this patient population [3]. Studies done since the 1950s have described the classic manifestations and risk factors of cryptococcosis in patients with cancer [3, 4]. Cryptococcosis has typically been described in patients with cancer who have impaired cell-mediated immunity and who receive high doses of steroids [1–6]. In addition, studies done before the 1990s emphasized the poor outcome associated with this mycosis in patients with cancer, with reported rates of treatment failure that were as high as 57%–85% despite therapy with amphotericin B [3, 7]. This is in contrast to the better outcome of patients with cryptococcosis who have AIDS or who have received organ transplants [5, 7, 8]. Nevertheless, all recent studies of cryptococcosis in patients with cancer consist of case reports or small case series [9–11]. The purpose of this study was to review our experience with cryptococcosis in patients with malignancy and no known HIV infection during the period of 1989–1999 at the University of Texas M. D. Anderson Cancer Center (Houston).

METHODS

Cases of cryptococcosis were identified by a review of the histopathology and microbiology culture reports from 1 January 1989 through 31 December 1999. The histological diagnosis of cryptococcosis was established by identification of the characteristic encapsulated yeasts by use of periodic acid–Schiff, mucicarmine, or Grocott-Gomori–methenamine silver nitrate staining. The microbiological diagnosis of C. neoformans was confirmed by use of standard methods [12]. Cryptococcal antigen
was detected by use of a latex agglutination–based antigen detection kit (Meridian Diagnostics).

We retrospectively reviewed the medical records of patients and obtained information regarding their underlying malignancy, risk factors, clinical signs and symptoms, diagnostic evaluation, prophylaxis, treatment, and outcome. Patients were excluded if they had known HIV infection or AIDS or were found to have no underlying malignancy. We also excluded patients whose samples of blood or CSF tested positive for cryptococcal antigen but for whom culture or histopathology produced negative results or had not been done. “Disseminated cryptococcosis” was defined as an infection that involved 2 noncontiguous sites or an active infection in 1 site in association with cryptococcemia. “Isolated pulmonary or meningeval cryptococcosis” was defined as a microbiologically or histopathologically proven active infection in the corresponding site with or without associated seropositivity for cryptococcal antigen (but with negative results of blood culture for C. neoformans).

Potential risk factors for cryptococcosis were defined as follows: lymphopenia (<500 lymphocytes/mm³), neutropenia (<500 neutrophils/mm³), and significant steroid use (cumulative dose of >250 mg of a prednisone equivalent in the 1 month before onset of infection). “Response to antifungal therapy” was defined as the resolution or improvement of all signs, symptoms, microbiological and serological abnormalities, and radiographic changes caused by infection. “Failure” was defined as a deterioration of the patient’s condition, as judged by clinical features and radiographic abnormalities, that resulted in death. Cryptococcosis was considered a contributory cause of death at autopsy if there was histopathologic involvement of a major organ and antemortem evidence of severe dysfunction of the affected organ.

Categorical data were analyzed by means of χ² or Fisher’s exact test, with use of Epi Info, version 6.04 (Centers for Disease Control and Prevention). P < .05 was considered statistically significant.

RESULTS

Of the 42 patients with culture results that were positive for C. neoformans, 11 were not included in the analysis (6 patients had lymphoma associated with AIDS; 4 had pulmonary cryptococcosis that mimicked lung cancer, but no underlying malignancy; and 1 patient with cancer had asymptomatic colonization of the Airways without any evidence of pneumonia). Nineteen additional patients with cancer tested positive for cryptococcal antigen in either CSF specimens (12 patients) or serum samples (7 patients) but lacked mycological confirmation and were not included in the analysis. We focused mainly on the cohort of those 31 patients with cancer who had culture-proven cryptococcosis (representing an incidence of 18/100,000 admissions for the period of 1989–1999). The incidence of cryptococcosis noted at autopsy was 0.2% (3 of 1765 autopsies conducted during the study period). We found 19 cases of pulmonary cryptococcosis, 6 cases of disseminated cryptococcosis, 3 cases of meningitis, and 3 cases of other, less-common clinical forms of cryptococcosis (panniculitis, cryptococcemia, and urinary tract infection in 1 patient each; table 1). Hematologic malignancy, especially lym-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median age, y (range)</td>
<td>52 (22–88)</td>
</tr>
<tr>
<td>No. male/no. female</td>
<td>18/13</td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other hematologic malignancies</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (16)</td>
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<tr>
<td>Chemotherapy ≤1 mo. before diagnosis</td>
<td>17 (55)</td>
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<tr>
<td>Steroids ≤1 mo. before diagnosis</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Median total cumulative dose, mg (range)</td>
<td>920 (266–4020)</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Meningeal</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Time of diagnosis</td>
<td></td>
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<tr>
<td>Antemortem</td>
<td>29 (94)</td>
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<tr>
<td>Postmortem</td>
<td>2 (6)</td>
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<tr>
<td>Treatment outcome</td>
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<tr>
<td>Response</td>
<td>23 (82)</td>
</tr>
<tr>
<td>Failure</td>
<td>5 (18)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients with characteristic, unless otherwise indicated.

* Chronic myelocytic leukemia, myelodysplastic syndrome, multiple myeloma (in 1 patient each).

° Renal (in 3 patients), breast (in 2); lung, stomach, ovarian, colon, pancreatic, endocrine tumor (in 1 each).

Prednisone equivalence.

b Meningitis and cryptococcemia (in 2 patients); meningitis, cryptococcemia, and pulmonary cryptococcosis (in 1); pulmonary cryptocoecosis and cryptococcemia (in 1); cryptococcemia and multiple skin lesions (in 1); cryptococcemia and urinary tract infection (in 1).

c Cryptococcemia, urinary tract infection, panniculitis (in 1 patient each).

d Three patients did not receive therapy.
phoid malignancy, was present in 20 (65%) of 31 patients with cryptococcosis (table 1). The majority of patients with cryptococcosis had lymphopenia (19 [61%] of 31 patients) at the onset of their infection, whereas only a minority had neutropenia (5 [16%] of 31). Seventeen (55%) of the 31 patients received chemotherapy during the month that preceded the diagnosis of cryptococcosis. Fludarabine, which causes substantial T cell dysfunction [13], was administered to 5 (36%) of 14 patients with cryptococcosis. Fludarabine, which causes substantial T cell dysfunction [13], was administered to 5 (36%) of 14 patients with non-Hodgkin’s lymphoma or chronic lymphocytic leukemia. Sixteen (52%) of the patients had received a significant steroid dose (median total dose, 920 mg; range, 266–4020 mg) before the onset of infection. In 1 patient, cryptococcosis complicated an allogeneic bone marrow transplantation. Fourteen (45%) of 31 patients had concomitant infections that occurred during cryptococcosis (in 5 patients) or within 1 month before the diagnosis of cryptococcosis. The majority of patients with cryptococcosis had lymphopenia (19 [61%] of 31 patients) at the onset of their infection, whereas only a minority had neutropenia (5 [16%] of 31). Seventeen (55%) of the 31 patients received chemotherapy during the month that preceded the diagnosis of cryptococcosis. Fludarabine, which causes substantial T cell dysfunction [13], was administered to 5 (36%) of 14 patients with non-Hodgkin’s lymphoma or chronic lymphocytic leukemia. Sixteen (52%) of the patients had received a significant steroid dose (median total dose, 920 mg; range, 266–4020 mg) before the onset of infection. In 1 patient, cryptococcosis complicated an allogeneic bone marrow transplantation. Fourteen (45%) of 31 patients had concomitant infections that occurred during cryptococcosis (in 5 patients) or within 1 month before the diagnosis of cryptococcosis (in 9 patients; range, 1–28 days). Infections associated with T cell dysfunction in particular, such as herpesviruses (in 4 patients; varicella-zoster virus and herpes simplex virus were present in 2 patients each), invasive molds (in 2 patients), and Listeria monocytogenes (in 1 patient), were common.

Of the 19 patients with pulmonary cryptococcosis, 13 (68%) had symptoms, whereas the remaining 6 (32%) were asymptomatic (4 patients had hematologic malignancies and 2 patients had solid tumors). For the 13 patients with symptomatic pulmonary cryptococcosis, the clinical presentation was nonspecific and included fever (in 7 patients; 6 other patients were afibrile while receiving systemic steroids) and respiratory abnormalities, such as dyspnea (in 7 patients), cough (in 7 patients), pleuritic chest pain (in 3 patients), and acute respiratory failure (in 2 patients). No patient had hemoptysis. The radiographic findings in cases of pulmonary cryptococcosis revealed a multitude of patterns, such as patchy opacities (in 6 patients), nodules (in 6 patients), widespread infiltrates (in 5 patients), or focal consolidation (in 2 patients). No patient had cavitation or interstitial pneumonia revealed by chest radiograph. The clinical presentation was frequently presumed to be primary lung cancer (in 6 patients), metastatic lung cancer (in 5 patients), lung nodules of unclear significance (in 6 patients), and pneumonia caused by an unknown pathogen (in 7 patients).

Table 2 shows the diagnostic yield of the invasive procedures (fine-needle aspiration, open lung biopsy, and bronchoalveolar lavage) used for the 19 patients with cancer who had pulmonary cryptococcosis. All invasive methods were found to have a very good diagnostic yield, especially when specimens were used for culture, which enabled the clinician to establish the diagnosis in 18 (95%) of 19 cases. No patient with pulmonary cryptococcosis had meningeal signs. All 11 patients with pulmonary cryptococcosis who underwent a lumbar puncture had negative results of studies of CSF specimens. Finally, of the 16 patients with pulmonary cryptococcosis tested for serum cryptococcal antigen, only 6 (38%) had a positive titer (median, 1:64; range, 1:2 to 1:256).

Five patients had cryptococcal meningitis (isolated in 3 patients and part of a disseminated cryptococcosis in 2 patients). The presenting signs and symptoms of meningitis were headache (in 5 patients), altered mental status (in 5 patients), fever (in 4 patients), cranial nerve deficits (in 4 patients), nausea and vomiting (in 3 patients), nuchal rigidity (in 2 patients), and seizures (in 1 patient). Studies of CSF specimens revealed the following results: median opening pressure, 32.5 mm H2O; WBC count, 77 cells/dL (range, 1–200 cells/dL); glucose level, 37 mg/dL (range, 20–66 mg/dL); and protein level, 133 mg/dL (range, 33–240 mg/dL). All patients with cryptococcal meningitis tested positive for cryptococcal antigen in CSF specimens (median titer, 1:256; range, 1:32 to 1:2048) and for cryptococci by India ink stain and by culture (median time to culture positivity, 5 days). In no case did a patient with cancer who had cryptococcosis but not meningeal symptoms have a positive result of a culture of a lumbar puncture CSF specimen. In no case did a patient with cryptococcal meningitis also have intracerebral cryptococcal lesions revealed by CT or MRI. Again, the diagnosis of cryptococcal meningitis was rarely sus-
pected, and the presentation was often presumed to be metastatic brain tumor, leptomeningeal disease, cerebrovascular accident, or bacterial meningitis.

With regard to the patterns of dissemination in the 6 cases of disseminated cryptococcosis encountered in our series, 2 patients had meningitis and cryptococcemia; 1 patient had meningitis, cryptococcemia, and pulmonary cryptococcosis; 1 patient had pulmonary cryptococcosis and cryptococcemia; 1 patient had cryptococcemia and multiple skin lesions; and 1 patient had cryptococcemia and urinary tract infection. Finally, 3 patients had unusual presentations of cryptococcosis. One was a male patient with vipoma and iatrogenic Cushing’s syndrome who developed persistent nosocomial fungemia and thrombosis of the right subclavian vein. His condition declined rapidly despite having received systemic amphotericin B therapy. The yeast in the blood was identified as \textit{C. neoformans}. One additional patient had cryptococcal panniculitis, and another had an isolated positive result of urine culture.

A total of 19 patients with cryptococcosis had blood samples obtained for culture. Of those, 6 patients (32%; 5 patients with disseminated cryptococcosis and 1 patient with cryptococcemia) had cultures that yielded \textit{C. neoformans} at the time of onset or during the course of infection. Overall, the diagnosis of cryptococcosis was made antemortem in 29 (94%) of the 31 cases. Of the 3 patients with cryptococcosis who underwent autopsy, 2 had their infections diagnosed postmortem.

Only 2 of the patients with cryptococcosis were receiving antifungal prophylaxis (1 patient received fluconazole, 200 mg/day, and 1 patient received amphotericin B, 25 mg/day given iv) before onset of cryptococcosis. Of the 31 patients with cryptococcosis, 28 (90%) received various combinations of antifungal agents as initial therapy (amphotericin B alone in 4 patients, amphotericin B plus fluconazole and 5-flucytosine in 3 patients, amphotericin B plus 5-flucytosine in 2 patients, lipid formulations of amphotericin B in 3 patients, fluconazole alone in 13 patients, and another agent in 3 patients). The median duration of antifungal therapy in those 28 patients was 90 days (range, 14–486 days). Twelve patients received a regimen that contained amphotericin B as initial therapy. However, only 9 patients received amphotericin B without fluconazole as initial therapy (median duration of therapy, 12 days; range, 5–31 days). For the 13 patients who received fluconazole as initial therapy, the duration of therapy ranged from 21 to 245 days (median duration, 98 days). Ten patients received fluconazole at 400 mg/day, 2 at 600 mg/day, and 1 at 200 mg/day. Of the 3 patients who did not receive any antifungal therapy, the infection was diagnosed postmortem in 2 patients and 1 patient was lost to follow-up. Antifungal treatment failed for only 5 (18%) of 28 patients. Failure was uncommon when the initial therapy was amphotericin B based (with or without 5-flucytosine, but without concomitant fluconazole; 3 of 9 patients experienced treatment failure) or fluconazole based (1 of 13 patients; \( P = .4 \)). No relapses of cryptococcosis were encountered.

Cryptococcosis was determined to have contributed to death in all 5 patients who experienced treatment failure, a rate of 26% (only 19 case records contained information about the cause of death). All patients who died of cryptococcosis had lymphopenia (\( P = .06 \)) and concurrent infections (\( P = .01 \)). In the remaining patients with cryptococcosis who responded to antifungal therapy, no relapse was encountered. Of note, 5 bone marrow transplantation procedures (4 allogeneic and 1 autologous) were subsequently done in 4 patients with hematologic malignancies and a history of cryptococcosis that preceded transplantation (1, 1, 5, 9, and 12 months before transplantation). All 5 patients had objective evidence of inactive cryptococcosis before transplantation, and all received antifungal prophylaxis (3 received fluconazole, 200 mg/day, 1 received fluconazole, 800 mg/day, and 1 received amphotericin B, 0.5 mg/kg/day given iv) throughout the preengraftment period. None of the 5 patients had recurrence of cryptococcosis after transplantation.

**DISCUSSION**

To our knowledge, this is the largest series of cryptococcosis cases in patients with cancer from a single institution in the 1990s. Most patients in this series had immunologic defects that are typically associated with cryptococcosis, such as lymphopenia and immune dysfunction due to prior steroid or fludarabine use [1–14]. As in older series, hematologic malignancies, especially lymphoma, were predominant [1–5].

Cryptococcosis remained a relatively uncommon disease in our institution during the study period; it was identified at autopsy in only 0.2% of the patients. This is consistent with similarly low rates of cryptococcosis found at autopsy in patients with cancer that are reported in international autopsy surveys [15, 16]. The low incidence of cryptococcosis could be partially due to the routine use of antifungal agents as prophylaxis or as empirical therapy in many patients with cancer who are at risk for cryptococcosis.

The presentation of cryptococcosis was nonspecific and mimicked that of other common entities, both infectious and noninfectious, seen in our institution. Pulmonary cryptococcosis was the predominant presentation. In some cases, pulmonary cryptococcosis mimicked acute respiratory failure. However, cases of acute respiratory failure due to cryptococcosis were much less common in patients with cancer than they were in patients with AIDS [17]. No unusual radiographic presentations of pulmonary cryptococcosis, such as interstitial pneumonia [18], were seen. As our study and others [19] suggest, a high index of suspicion is needed to diagnose pulmonary cryptococcosis in patients with cancer. Moreover, a clinical pic-
tured compatible with lung metastasis in a patient with known malignancy should always persuade the clinician to attempt to establish a definite diagnosis, especially because the diagnostic yield of invasive pulmonary procedures in this series was found to be very good. Patients with meningeal involvement had prominent neurological symptoms and defects. This was not unexpected, because cryptococcal meningitis in patients with cancer rarely occurs in the absence or near-absence of neurological signs and symptoms [20, 21]. On the other hand, our study was in agreement with a recent report that the performance of lumbar puncture in patients without HIV who have pulmonary cryptococcosis but no neurological symptoms may not always be warranted [22]. Finally, we saw some unusual presentations of cryptococcosis that have been previously described by others, including cryptococcemia that mimicked nosocomial acute candidiasis [23] and cryptococcal cellulitis that mimicked nonspecific panniculitis [24].

In contrast to other, less recent reports [2–4, 7], the present series of patients with cancer who had cryptococcosis did not seem to have a high mortality rate that was attributable to cryptococcosis. The favorable outcome seen among patients in our series may be partially explained by the relatively young patient age and the predominance of the pulmonary form of cryptococcosis, which generally has a better prognosis than do disseminated and meningeal forms of the disease [6, 7, 25]. The good prognosis in our series may be further explained by the relatively frequent follow-up and aggressive evaluation that our patients generally received, which led in turn to earlier diagnosis, prompt initiation of antifungal treatment, and avoidance of dissemination. Lack of treatment of asymptomatic or minimally symptomatic pulmonary cryptococcosis has been reported to result frequently in disseminated infection [14]. Finally, it appears that markers of severe immunosuppression, such as lymphopenia and concomitant infections, indicate a poor prognosis, as reported elsewhere [23, 26]. The small number and heterogeneity of cases in our series precluded multivariate analysis of many independent prognostic variables, which might have provided more definitive answers.

There was a trend toward better efficacy of fluconazole when it was used as initial treatment for cryptococcosis in our series. However, this trend was most likely due to selection bias, because our study was uncontrolled, the pulmonary form of the infection predominated, and patients who were the most ill were given amphotericin B-based treatment initially. In addition, evaluation of the merit of novel therapeutic strategies, such as lipid formulations of amphotericin B or combination therapy, was again hampered by the small number and heterogeneity of cases in our series. Several recent reports of uncontrolled studies describe successful outcomes in patients with cryptococcosis who received treatment with fluconazole or lipid formulations of amphotericin B, especially for pulmonary cryptococcosis [27–31]. The optimal duration of treatment of cryptococcosis in patients with cancer is also unclear [7]. However, the experience in this institution seems to indicate that long-term suppression is unnecessary, on the basis of the fact that no relapses were encountered. Most of our patients (75%) did not receive >4 months of therapy. Finally, our results suggest that adequately treated cryptococcosis should not preclude subsequent bone marrow transplantation, because no such patient who was adequately treated for cryptococcosis experienced relapse during the posttransplantation period. However, effective secondary prophylaxis seems critical to a successful outcome for those patients.

In conclusion, in the 1990s, cryptococcosis remained a rare mycosis manifesting itself pleiotropically in patients with cancer. Since the diagnostic yield and therapeutic outcome for such patients are good, every effort should be made to obtain a timely diagnosis.

Acknowledgments

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References