Coccidioidomycosis in Patients With Hematologic Malignancies

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Background: An endemic fungal infection of the desert southwestern United States, coccidioidomycosis is generally a self-limited illness in healthy persons. Immunosuppressed persons who contract coccidioidomycosis, however, are at increased risk for disseminated infection.

Methods: We conducted a retrospective review of patients with coccidioidomycosis and hematologic malignancy or bone marrow disease.

Results: Fifty-five patients were identified. The most common underlying malignancies were non-Hodgkin lymphoma and chronic lymphocytic leukemia. Extrathoracic (or disseminated) infection was observed in 12 patients (22%). Fifteen patients (27%) died with active coccidioidomycosis. Treatment of the hematologic disease with corticosteroids or antineoplastic chemotherapy increased the risk of death.

Conclusion: To date, this is the largest case series of patients with hematologic malignancy and coccidioidomycosis. In persons with hematologic malignancy, coccidioidomycosis can be a severe illness with a high risk for disseminated infection and death.

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Infection with Coccidioides immitis occurs in the desert regions of the southwestern United States, in adjacent regions of Mexico, and in other areas of Central and South America. Primary infection with C immitis is generally limited to the lungs, and most immunocompetent patients have mild to moderate symptoms. Extrapulmonary, or disseminated, infections are less common forms of coccidioidomycosis found more frequently among patients who are African American, Filipino, pregnant, or immunosuppressed.

Previous reports have indicated that coccidoidal infection was often disseminated and frequently fatal in patients with hematologic malignancies. However, most of these reports were hampered by a small number of cases. In addition, they may be less relevant now because of recent changes in diagnostic studies and treatment methods for both coccidioidomycosis and hematologic malignancies. Therefore, we reviewed our experience with patients who had coccidioidomycosis and hematologic malignancies and were seen at Mayo Clinic over a 25-year period. Most cases were identified after the Arizona facility opened in 1987.

Methods

A retrospective medical chart review was conducted at Mayo Clinic facilities in Scottsdale, Ariz, and Rochester, Minn. Patients were identified through a search for coccidioidomycosis or valley fever in the institution’s master diagnosis sheet and code databases of the International Classification of Diseases, Ninth Revision (ICD-9). These patients were then cross-referenced against a database of patients who had leukemia or lymphoma (chronic lymphocytic leukemia [CLL], Hodgkin lymphoma, non-Hodgkin lymphoma [NHL], chronic myelogenous leukemia [CML], hairy cell leukemia or acute leukemias), multiple myeloma (MM), or undifferentiated or not further classified myelodysplastic and myeloproliferative disorders. Search dates were between January 1987 and September 2002 for the Scottsdale facility and between January 1977 and February 2002 for the Rochester facility.

To obtain demographic and clinical data, we reviewed all charts. Variables included hematologic diagnosis, age, sex, coexisting illness, type of treatment for the hematologic disorder, use of corticosteroids or radio-
therapy, adjunctive treatment techniques (eg, use of colony-stimulating factors or erythropoietin), or splenectomy. For information about the coccidoidal infection, we also abstracted the method of diagnosis, extent of coccidioidal infection, we also abstracted the method of diagnosis, extent of disease; diabetes mellitus was a comorbid illness in 8 (15%) of the 55 patients. Mean length of follow-up was 40 months (range, 1-240 months).

The underlying malignancy varied (Table 2): 43 patients (78%) received antineoplastic chemotherapy and 34 (62%) received corticosteroid therapy.

METHOD OF DIAGNOSIS AND SEROLOGIC RESULTS

Many patients had multiple and often concurrent culture and histopathologic evaluations, and 43 had definite coccidioidomycosis. *Coccidioides immitis* was isolated from sputum in 9 patients (16% of the entire series), from bronchoscopy in 10 patients (18%), and from biopsy in 2 patients (4%). Spherules consistent with *C immitis* were present in transthoracic needle biopsy specimens in 4 patients (7%), in open surgical excisions or biopsy specimens of lung tissue in 9 patients (16%), and in biopsy specimens of extrapulmonary sites in 5 patients (9%). The diagnosis of coccidioido-

Several conditions were also compared among other variables: death with active coccidioidomycosis, the presence of extrathoracic infection, and treatment with any type of chemotherapy or with corticosteroids in particular. The Pearson $\chi^2$ statistic was used in the statistical assessment of the comparison of proportions.

The margin of error for each comparison was obtained by calculating the 95% confidence interval for the differences between the group proportions.
mycosis was confirmed histopathologically in 5 autopsy cases.

Probable coccidioidomycosis was diagnosed in 12 patients (22%).

For the 38 patients who had serologic tests, immunoassay or complement fixation tests were positive in 21 (55%). Of the 17 patients with initially positive complement fixation tests, 15 (88%) had a titer of 1:8 or less. Coccidioidal antibody was demonstrable in most patients with NHL and MM in whom tests were performed but was detected in only 3 (33%) of 9 patients with CLL (Table 3).

ONSET OF INFECTION

Coccidioidomycosis preceded the diagnosis of a malignancy in 8 (15%) of the 55 patients. One of these patients had a reactivation of coccidioidomycosis after the diagnosis of NHL although he did not receive chemotherapy or corticosteroids. None of the other 7 patients experienced recurrent coccidioidal infection; of them received long-term suppressive antifungal therapy because of preexisting coccidioidal meningitis.

In 75% of the patients in our series, the coccidioidal infections occurred after the diagnosis of malignancy. The mean interval from the diagnosis of cancer to coccidioidomycosis was 51 months (range, 1-264 months). Four patients (7%) presented for medical attention with concurrent coccidioidal meningitis. Pulmonary involvement was present in 52 patients (95%), 2 (4%) of whom had positive blood cultures but no other extrapulmonary infection. Nine (17%) of the 52 patients had disseminated infection. The sites of dissemination included the skin (7% of all patients), the central nervous system (4%), and single-organ involvement (liver, kidney, bone marrow, pericardium, testicle, or bone). Three (5%) of the 55 patients had disseminated infection with no evidence of pulmonary coccidioidomycosis.

On radiographs, infiltrates were unifocal in half of the patients with pulmonary infection, regardless of whether disease was limited to the chest or disseminated.

No statistical association could be demonstrated between disseminated infection and such identifiable risk factors as type of malignancy, treatment provided for malignancy, or sex.

COCCIDIOIDOMYCOSIS IN SPECIFIC HEMATOLOGIC MALIGNANCIES

Table 3 summarizes selected characteristics of patients who had specific hematologic malignancies. Patients who had CLL, NHL, MM, or CML were compared with respect to the presence of thoracic or extrathoracic coccidioidal infection, serologic test findings, clinical resolution of infection, or death attributed to infection.

Of the 17 patients with CLL, 16 (94%) had disease limited to the lungs and 5 (29%) died. Three (33%) of the 9 CML patients who were treated had positive results on coccidioidal serologic tests.

Of the 17 patients with NHL, 11 (65%) had infection limited to the lungs, 6 (35%) had extrapulmonary infection, and 5 (29%) died. Eight (62%) of the 13 patients who were tested had positive results on coccidioidal serologic tests.

TREATMENT OF COCCIDIOIDOMYCOSIS

Of the 55 patients who had coccidioidomycosis, 44 (80%) received medical, surgical, or combined antifungal treatment. 3 were treated with surgical resection of a pulmonary focus without medical therapy, and 2 required surgical resection when medical therapy alone was inadequate to control infection.

Mortality was high among those treated with antifungal therapy...
alone. Four of 8 patients who received amphotericin B as their sole antifungal therapy died with active coccidioidal infection; 3 of 23 patients who were treated with only imidazole antifungal medication died with active infection; 3 of the 5 patients in whom amphotericin B treatment was instituted after a failing course of fluconazole died with active infection; and 1 of the 5 patients who were treated initially with amphotericin B, and then with fluconazole, died with active infection.

The cumulative doses of amphotericin varied widely, ranging from 300 mg to 2 g, but did not correlate with patient outcome. Fluconazole, primarily 400 mg daily, was used in 32 (89%) of 36 patients who received imidazole treatment.

Eleven patients did not receive any antifungal therapy. In 4 of these 11 patients, coccidioidomycosis was diagnosed post mortem and in the other 7, the coccidioidal infection resolved without relapse. One of these 7 patients had an infection that occurred before malignancy, and 5 had mild malignancies that did not require chemotherapy.

**Mortality**

Of the 55 patients, 40 (72%) survived during the follow-up period. Of the 16 patients who died, 15 died with active coccidioidomycosis. Potential risk factors contributing to death with coccidioidomycosis included the type of malignancy, the use of chemotherapy (including corticosteroids), the presence of extrathoracic infection, and male sex. Chronic myelogenous leukemia (vs other malignancies, P = .01), the use of any chemotherapy (P = .02), and the use of corticosteroids (P = .02) were all statistically significant factors associated with mortality.

**Comment**

This review of 55 patients with coccidioidomycosis and hematologic malignancy represents the largest series reported to date. Most of these infections occurred in patients with NHL and CLL. Because these malignancies also constitute the majority of hematologic malignancies in our institution's cancer registry as a whole, NHL and CLL did not appear to be disproportionately represented among patients infected with C immitis. The immunologic basis for coccidioidal infection in patients with hematologic malignancy is unclear. Certainly, deficiency of T-lymphocyte function is important, and patients with hematologic malignancies have multiple points of immunologic impairment, either because of disease or because of chemotherapy. Advancing age seems to be a risk factor for symptomatic infection, and the elderly patients in our series were typical of the advanced age of the population seen at our institution in general.

For most of our patients, infections were first recognized months or years after the diagnosis of a hematologic malignancy. Although it is impossible to state definitively that coccidioidal infection was acquired at or near the time of diagnosis, only 1 patient appeared to have a reactivation of a previous infection. The patients who had a documented history of coccidioidal infection before the diagnosis of malignancy had no clinically evident recurrence of infection, even though immunosuppressive medications were administered in the absence of concomitant antifungal medication. Previous reports of coccidioidomycosis in association with hematologic malignancy have emphasized reactivation of infection. We cannot explain the discrepancy between these observations and ours, but it is likely that multiple factors contribute, including patient selection, type and treatment of malignancy, duration of follow-up, and the possibility that antifungal therapy for the treatment of primary coccidioidomycosis prevented reactivation.

Coccidioidomycosis in patients with hematologic malignancies is associated with considerable morbidity and mortality. Disseminated infection was found in more than 20% of the patients in our series, far exceeding the observed rate of 1% to 2% in immunocompetent persons. Pulmonary infection alone was associated with a mortality rate of 27% during follow-up. Worse still, 50% of the patients with disseminated coccidioidomycosis died.

Risk factors for disseminated infection and death were difficult to identify among specific hematologic malignancies or treatment regimens. Although small sample sizes made analysis difficult, a few risk factors could be identified. Univariate analysis showed that overall mortality was greatly increased by corticosteroid treatment or antineoplastic therapy. Also, although only 3 patients in the series had CML, all died with active coccidioidal infection; compared with other malignancies, this association achieved statistical significance (P = .01).

Attributable mortality could not be assessed from our retrospective analysis. Many patients died with concurrent malignancy and coccidioidomycosis, and the outcome in others could not be specified when their care was transferred to hospice management.

A comment should be made about the diagnosis of coccidioidal infection. The common problems of fever and pulmonary infiltrates in patients with malignancy are compounded by chemotherapy-induced neutropenia and possibly drug-induced toxic effects in the lung. It is possible that patients with hematologic malignancies acquired coccidioidal infection that escaped recognition. In some patients, the infection may have resolved spontaneously, and in others, it may have been treated empirically with antifungal agents without a specific diagnosis. Also, some patients may have died of coccidioidomycosis without the infection being recognized, because autopsies may not be performed in this group of patients. Because our series is retrospective, we had to rely on the treating physicians' consideration of coccidioidomycosis in the differential diagnosis. However, even in an area endemic for coccidioidomycosis, the diagnosis is not often considered, as evidenced by the fact that many patients in our own series never had coccidioidal serologic tests. Moreover, as our data show, the sensitivity of anticoccidioidal antibody tests varies in their sensitivity in patients with hemato-
logic malignancy—from poor (33% sensitive) in patients with CLL to good (83% sensitive) in patients with MM.

Treatment of coccidioidomycosis in our patients with hematologic malignancy was largely at the discretion of the treating physician and thus varied widely. As triazole therapy became available, treatment with amphotericin B decreased in frequency. Our therapy recommendations mirror the guidelines of the Infectious Diseases Society of America.7

In summary, this review of our experience with coccidioidomycosis in 55 patients with hematologic malignancies and myelodysplastic or myeloproliferative disorders found that disseminated infection was common. The mortality rate was high and associated with corticosteroid treatment and the use of antineoplastic chemotherapy.

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REFERENCES


