Coccidioidomycosis and Tuberculosis Coinfection at a Tuberculosis Hospital

Clinical Features and Literature Review

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Abstract: Tuberculosis (TB) and coccidioidomycosis can have similar clinical and radiologic presentations but require different treatments. Coinfection with TB and *Coccidioides immitis* is uncommonly reported and may be underdiagnosed in endemic areas.

We performed a retrospective review of the medical records of all patients admitted to a TB referral hospital between 1995 and 2007, and selected all cases of TB and coccidioidomycosis coinfection in patients aged 18 years or older. All admitted patients had a diagnosis of TB and had sputum cultures for both pathogens. We reviewed clinical, laboratory, and radiologic features of the cases, and noted antimicrobial treatments received and outcomes.

We identified 9 patients, of whom 7 (78%) were Hispanic. Most patients were male (8/9, 89%), and all were diagnosed with coccidioidomycosis after TB. Three (33%) patients had drug-resistant TB. Six patients had culture-positive TB at the time of the double diagnosis, and 2 patients developed active coccidioidomycosis during their hospital stay. Only 1 had human immunodeficiency virus/acquired immunodeficiency syndrome (HIV-AIDS) (CD4 count, 20 cells/mm^3). All but 2 patients were treated with antifungal agents. Two patients died, 1 of whom had AIDS. Radiologic studies were unable to distinguish between TB and coccidioidomycosis, except for a patient who developed a new air-fluid level in a previously stable cavity.

TB and coccidioidomycosis coinfection should be suspected in coccidioidomycosis-endemic regions among patients with TB who fail to improve clinically or radiologically despite adequate, culture-directed therapy.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, AUC = area under the curve, CDC = United States Centers for Disease Control and Prevention, COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, PPD = purified protein derivative, SD = standard deviation, TB = tuberculosis, TCID = Texas Center for Infectious Disease.

INTRODUCTION

Tuberculosis (TB) is a common disease in many developing countries. In 2006, Texas had a TB rate of over 6.7 cases per 100,000 population (overall United States case rate, 4.6 per 100,000).[5] A number of these cases are imported from neighboring Mexico, which has an even higher incidence of TB (up to 44.6 per 100,000 in the Mexican states immediately south of the Rio Grande).[5,28] Primary pulmonary TB infection is usually associated with focal radiographic infiltrates and ipsilateral hilar lymphadenopathy. Reactivation of pulmonary TB often presents with nodules and cavitation, especially in the upper lobes.[23]

Coccidioidomycosis is an endemic mycosis of South America, northern Mexico, and the southwestern United States, including Texas. In 2005, 6542 cases of coccidioidomycosis were reported to the United States Centers for Disease Control and Prevention (CDC), but as many as 150,000 cases of self-limited infection occur every year.[21,31] Patients with primary coccidioidomycosis may have a normal chest X-ray or focal infiltrates. Patients with chronic pulmonary coccidioidomycosis may develop cavities, hilar lymphadenopathy, and rarely, an intracavitary mycetoma. In patients with chronic progressive pulmonary coccidioidomycosis, the radiographic findings closely resemble pulmonary TB.[7,40]

Active TB disease and chronic pulmonary coccidioidomycosis share some common risk factors, including overlapping areas of endemicity (including south Texas) and increased occurrence among immunosuppressed patients. Furthermore, presenting syndromes may be similar, with protracted constitutional symptoms, respiratory symptoms, subacute meningitis, or reactivation of primary infection years to decades after initial exposure.[11,23,31]

While coinfection with TB and coccidioidomycosis has been described sporadically in the literature, most reports are over 30 years old.[3,8–10,12,15,16,18,19,22,27,29,33–36,41] Recently reported cases were discovered incidentally in a coccidioidomycosis case series.[26] Given similarities in the clinical presentation, the similar radiologic patterns of both infections, and the possible suppressive effect of TB therapy on the growth of *Coccidioides immitis,*[13] diagnosis of coinfection can be challenging. Furthermore, the decrease in case rates of TB in the United States may have caused a reduction in the number of recognized coinfections, although the potential effect of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV-AIDS) on coinfection has not been examined.[5,6]

We conducted the current study to describe the clinical, epidemiologic, laboratory, and radiologic features of patients with coccidioidomycosis and TB coinfection, and their outcomes. We present here the cases of coccidioidomycosis and TB coinfection managed at an inpatient TB reference center over 12 years, and we describe, for the first time to our knowledge, a detailed case series of symptomatic patients from Texas, a case of coinfection with multidrug-resistant TB and coccidioidomycosis, and a patient with TB, coccidioidomycosis, and HIV-AIDS.

PATIENTS AND METHODS

We conducted the current study as a retrospective review from the Texas Center for Infectious Disease (TCID) in San

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Antonio, TX. TCID is a 71-bed referral hospital for persons requiring inpatient TB treatment. We identified patients by searching medical records for cases with International Classification of Diseases (ICD)-9 diagnostic codes of TB and coccidioidomycosis from January 1995 to December 2007. Patients were included if they were older than 18 years old and had a diagnosis of both TB (by culture) and coccidioidomycosis (by cultures or histology).

Data obtained included demographic characteristics; city of origin; comorbidities; use of alcohol, drugs, and tobacco; presenting symptoms; clinical course; laboratory findings; and response to therapy. Response to therapy was defined as microbiologic, radiologic, clinical, and (when available) serologic improvement at the end of follow-up. Laboratory studies evaluated include those at admission to the hospital and at the time of diagnosis of coccidioidomycosis infection (including blood cell counts, HIV serology, CD4 lymphocyte counts, and coccidioidomycosis serologies), and studies relevant to define the diagnosis of TB disease and results of mycobacterium susceptibility testing. Radiology reports and images were described before diagnosis of coinfection, if available; at the time coinfection was diagnosed; and at the end of follow-up. Therapy for TB and coccidioidomycosis was recorded until the end of follow-up.

Literature Review

We performed a PubMed (National Library of Medicine, Bethesda, MD) search with the terms "coccidioidomycosis" and "tuberculosis," including the cases where both infections were present in the same patient, concomitantly or sequentially. We defined the cases as those diagnosed by histopathologic or microbiologic methods. Other cases reported in English or Spanish were also included. Cases where the diagnosis of coccidioidomycosis was made solely by serology were excluded.

Statistical Analysis

Due to the retrospective nature of this series and the limited number of cases, statistical analysis included descriptive methods only. Continuous variables were reported as the mean ± standard deviation (SD) and categorical variables as percentages. This study was approved by the Institutional Review Board from the University of Texas Health Center at Tyler.

RESULTS

We identified 9 patients in the retrospective record review. Clinical and demographic characteristics of patients, symptoms, and therapy for TB and coccidioidomycosis are available in Table 1. Patients were usually male (8/9, 89%), Hispanic (7/9, 66%), and middle-aged (mean age, 42 ± 14 yr). Although most patients (6/9) were originally from Texas, 3 patients were born in Mexico. Three patients were tobacco smokers, 3 were heavy alcohol drinkers, and 1 reported cocaine use. Comorbidities varied among patients, and AIDS was present in only 1 case. Four patients had underlying lung disease at the time of diagnosis, including chronic obstructive pulmonary disease (COPD) in 3 cases and bronchiectasis in 2 cases. Two patients had diabetes mellitus.

Risk factors for TB included AIDS (n = 1), incarceration (n = 2), homelessness (n = 2), and diabetes mellitus (n = 2). All patients had pulmonary TB, and 1 also had TB lymphadenitis. All patients were diagnosed with coccidioidomycosis after being diagnosed with TB; all patients were diagnosed by sputum fungal cultures and coccidioidomycosis serologies, which are routinely performed on all patients admitted to TCID. However, only 3 cases (33%) had positive fungal sputum smears. Two cases had evidence of new coccidioidomycosis infection during hospitalization, with initially negative serology and sputum fungal culture on admission. One case (Case 4) remained highly symptomatic despite treatment for TB and was therefore retested and found to have positive coccidioidomycosis serology and sputum culture 6 months after admission. He was ultimately diagnosed with COPD and bronchiectasis. The second case (Case 9) was under treatment for multidrug-resistant TB and developed new symptoms 2 years, 8 months after admission. She was found to have an air-fluid level inside a previously noted pulmonary cavity. Serologies and fungal cultures, initially negative on admission, were positive for *Coccidioides* species at the time the new symptoms developed. All patients had pulmonary coccidioidomycosis except 1 patient who had disseminated disease including coccidioidal meningitis (Case 1) in the setting of AIDS.

Laboratory findings are shown in Table 1. Anemia was common (present in 5 cases; mean hemoglobin, 11.9 ± 2.3 g/dL; reference value: 12–16 g/dL) but leukocytes were only mildly elevated (3 cases). All patients were screened with enzyme-linked immunosorbent assay (ELISA) for HIV 1–2, but only 1 tested positive and was proved to have AIDS with a CD4 lymphocyte count of 20 cells/mm^3. Four patients (45%) had negative sputum cultures for TB at the time of coccidioidomycosis diagnosis but all had positive sputum cultures for *Coccidioides* species.

Therapy included TB medications and an antifungal triazole in most cases. Three patients were managed with itraconazole. One of these was switched to fluconazole because he developed anterior uveitis on rifabutin and was switched to rifampin (Case 2). Four patients received fluconazole, and 2 patients received no specific treatment for coccidioidomycosis. Two patients died: 1 with AIDS and disseminated coccidioidomycosis (Case 1), and another who developed a new infiltrate and subsequent respiratory failure (Case 5).

Radiologic findings were similar to those of patients with pulmonary TB (see Table 1). In the cases with prior radiographs available, only 1 showed changes associated with the onset of symptoms: an air-fluid level appeared in a preexisting lung cavity (Case 9; Figure 1, A and B). The patient had already completed the therapy for multidrug-resistant TB. In this instance, the findings resolved following 12 months of treatment with itraconazole.

DISCUSSION

Coccidioidomycosis and TB are not frequently reported to cause coinfection. Over the previous 25 years, reports of TB and coccidioidomycosis coinfection have been uncommon. Papers published in the 1940s to 1960s described coinfection with greater regularity; however, the clinical presentations were diverse.[3,8–10,12,15,16,18,19,22,27,29,33–36,41] Published case reports included coccidioidal cavities thought to be secondarily infected by TB, and vice versa.[10]

All symptomatic patients reported had lived or worked in coccidioidomycosis-endemic areas. Most patients were reported or had lived in Arizona or California.[3,8–10,12,15,18,19,22,27,29,33–36]

In the present case series, TB and coccidioidomycosis coinfection was difficult to distinguish clinically and radiologically from TB or coccidioidomycosis monoinfection.[23,31] A few patients had persistent or relapsing symptoms despite receiving appropriate therapy for TB, and were subsequently found to have coccidioidomycosis coinfection.

Epidemiology and Demographic Characteristics

In our search of the literature, we identified 66 cases of proposed TB and coccidioidomycosis coinfection.[3,8–10,12,15,16,18,19,22,27,29,33–36,41]

TABLE 1. Characteristics of 9 Patients With TB and Coccidioidomycosis Coinfection

Case No. Age (yr)/Sex Racial/ Ethnic Group	History	Symptoms and Signs	Laboratory Findings	Radiologic Findings	Treatment	Outcome
1 47/M Hispanic	AIDS. Pulmonary TB diagnosed 1/2001 and disseminated CM 1/2002	Fever, cough, lymphadenitis, and weight loss improved with TB treatment. Later developed nausea, vomiting, and headache.	TB: sputum culture: pan-susceptible 11/2001. CM: 1/2002: sputum culture (−), immunodiffusion (+). Serum CF 1:1024, CSF CF (+). 6/2002: Sputum culture (+).	CXR 12/2001: diffuse bilateral pulmonary nodules. CT chest: miliary nodules, dense LLL consolidation, and necrotic mediastinal lymphadenopathy.	TB: INH, RFB, PZA. CM: fluconazole 800 mg daily	Altered mental status and death 6/2002.
2 36/M Hispanic	Pulmonary TB diagnosed 1/2000 and pulmonary CM 3/2000	Persistent cough, hemoptysis, weight loss, anorexia, night sweats, fevers up to 104 °F (40 °C) despite 2 mo of TB therapy.	TB: sputum culture: pan-susceptible 3/2000. CM: 3/2000: sputum cultures (+), stain (−). 2/2000: Serum CF (−), then (+) at 1:4 3/2000.	CXR 2/2000: RUL volume loss with tracheal deviation, thick-walled cavities in RLL. LLL fibrosis. Regression in 7/2001. CT chest 3/2000: RUL and RLL superior segment volume loss, consolidation, air bronchograms, and cavities. L lung infiltrates, hyperexpansion, and a 1.8 cm cavity.	TB:, PZA, INH, EMB, RFB (then RIF*) CM: itraconazole 600 mg daily x 1 mo*, then fluconazole 600 mg daily in 5/2000.	Clinical and radiological improvement. Left hospital on 8/2/2000.
3 37/M Hispanic	DM. Pulmonary TB diagnosed 1/1995 and pulmonary CM 6/1995	Hemoptysis for 1 yr, pleuritic chest pain for 3 mo, subjective fevers and dyspnea.	TB: sputum culture: INH resistant 6/1995. CM: 6/1995: sputum stain (−), culture (+). Serum qualitative IgG (+); quantitative (−) (<1:2) 8/1995.	CXR 6/1995: fibronodular infiltrates of ULs and superior segments of LLs. Thin-walled cavities in ULs, R>L hilar enlargement. Repeat CXR 2/1996: slight improvement of LUL disease.	TB: RIF, ciprofloxacin, amikacin, PZA. CM: none.	Radiographic and clinical improvement, Discharged on 2/16/1996.
4 36/M White	Homeless, COPD and bronchiectasis. Pulmonary TB diagnosed 1/1997 and pulmonary CM 7/1997	Productive cough, fever, chills, night sweats, 23 kg (50 lb) weight loss. No improvement on TB therapy.	TB: Sputum culture (+), pan- susceptible 1/1997. CM: 1/1997: sputum culture (−). 7/1997: (+) sputum stain and culture. Serologies (−) 1/1997. Serum qualitative CF (+) 8/1997, quantitative CF 1:16 1/1998.	CXR 1/1997: diffuse bilateral fibronodular and patchy infiltrates, cavities, bulla, pleural thickening. Repeat CXR 7/1997: regression of infiltrates and of pleural thickening.	TB: INH, RIF, EMB, PZA. CM: fluconazole 800 mg daily.	Radiographic and clinical improvement. Discharged home.
5 39/M Hispanic	DM. Pulmonary TB diagnosed 1/1994 in Mexico and then again 1/1997. Pulmonary CM diagnosed 3/1997	Persistent cough with hemoptysis, fever.	TB: sputum culture (+), resistant to RIF, INH, EMB, and ETH 3/1997. CM: 3/1997: sputum stain and culture (+). Serum CF 1:32, CSF CF negative 3/1997, 1 mo later serum CF (−).	CXR 3/1997: pleural thickening, scattered consolidations, marked volume loss and destruction of both ULs. CT chest: bilateral UL destruction and cavitation. LLL atelectasis. Fibronodular infiltrates.	TB: amikacin, EMB, PZA, ofloxacin, cycloserine CM: itraconazole 200 mg twice daily.	Sudden onset respiratory distress; ICU transfer and death on 4/23/1997.

6	55/M White	Alcoholism, COPD, and smoking. Pulmonary TB diagnosed 1/1998 and pulmonary CM 7/1998	Cough.	TB: sputum culture: pan-susceptible 1/1998. CM: 8/1998: sputum cultures (+) and stains (−). Serum qualitative CF (+) but quantitative (−) 8/1998. 1/1998: serum CF 1:2.	CXR 8/1998: hyperexpansion, bilateral UL fibronodular, linear, and L>R calcific opacities. Moderate CXR improvement 3/1999. CT chest 9/1998: nodules throughout both ULs and superior segment of LLL, some with stellate appearance, many with calcification, 1 with cavitation. Bullae in ULs.	TB: INH, RIF, PZA, EMB CM: fluconazole 400 mg daily.	Discharged home. Cured TB.
7	24/M Hispanic	Pulmonary TB diagnosed 1/1994 and pulmonary CM 4/1997	Hemoptysis x 3 yr, chills, 60 kg (132 lb) weight loss, dyspnea on exertion for 2 mo, pleuritic chest pain.	TB: sputum smear and culture (+), resistant to SM, INH, ETH, RIF, EMB, and RFB 4/1997. CM: 4/1997: sputum stain (−), culture (+). 4/1997: serum CF 1:2, 10/1997: serum CF 1:4.	CXR 4/1997: L lung replaced by bullae, LLL atelectasis. R lung hyperexpanded, extensive fibronodular and patchy infiltrates throughout. 3.0 cm cavity in RUL. Pleural thickening R apex. Unchanged 1/1998. CT chest 4/1997: L lung: destroyed and replaced with bronchiectasis, pleural thickening, and effusion. Markedly hyperexpanded R lung, with cavities, largest 3.3 cm, and fibronodular infiltrates, greatest in UL.	TB: amikacin, PZA, ofloxacin, CPM, clofazimine. CM: fluconazole 400 mg daily.	Left hospital 1/1998.
8	73/M Hispanic	Homeless, dementia, COPD, and alcoholism. Pulmonary TB diagnosed 10/1998 and pulmonary CM 11/1998	23 kg (50 lb) Weight loss, fever, and malaise.	TB: sputum culture (+), pan-susceptible 10/1998. CM: 11/1998: sputum stain (−), culture (+). Serologies (−) 11/1998 then serum CF 1:4 1/1999.	CXR 11/1998: hyperexpanded lungs, 3 large cavities, largest 5.2 cm, 2 with air-fluid levels. Fibronodular infiltrates, greater in ULs. CXR 12/1999: regression of fibronodular infiltrates and cavities; resolution of air-fluid levels. CT chest 11/1998: fibronodular infiltrates RUL and RML, several cavities, largest 5.2 cm. Low-density liver lesions.	TB: INH, RIF, PZA, EMB. CM: none.	Left hospital 5/1999.

(continued on next page)

TABLE 1. Characteristics of 9 Patients With TB and Coccidioidomycosis Coinfection

Case No. Age (yr)/ Sex Racial/ Ethnic Group	History	Symptoms and Signs	Laboratory Findings	Radiologic Findings	*Treatment	Outcome
9 33/F Hispanic	Pulmonary TB diagnosed 12/1985, underwent unknown therapy followed by relapse with MDR-TB 1/2004. Pulmonary CM diagnosed 9/2006	Recurrent productive cough, fever, chills, chest pain, anorexia, weight loss.	TB: sputum culture (+) 1/2004, resistant to INH, EMB, RIF, RFB, ETH. Cured of TB at time of CM diagnosis. CM: 10/2006: sputum stain (−), culture (+). 1/2004: serum CF (−). 9/2006: serum CF 1:4.	CXR 1/2004: R lung with air trapping, diffuse lucent changes, scarring, volume loss, 2.5 cm cavity RUL, large R-sided density. L base cystic and dense parenchymal changes, 3.5 cm cavity in LLL. CXR 9/2006: development of air-fluid level in preexisting LLL cavity. CT chest 1/2004: RLL and LLL. LUL bronchiectasis, thick-walled cysts. RLL collapse. RML and RLL with cavities and cysts. Small L pleural effusion. 12/2006: Cavitary lesion in LLL shows interval development of air fluid level.	TB: amikacin alternating with CPM for 1 yr and CS, PAS, CF, MOXI and linezolid for 27 mo. CM: itraconazole 200 mg twice daily for 1 yr.	Symptomatic improvement.

Abbreviations: CF = complement fixation, CM = coccidioidomycosis, CPM = capreomycin, CSF = cerebrospinal fluid, CT = computed tomography, CXR = chest X-ray, DM = diabetes mellitus, EMB = ethambutol, ETH = ethionamide, INH = isoniazid, L = left, LL = lower lobe, MDR = multidrug-resistant, ML = middle lobe, PZA = pyrazinamide, R = right, RFB = rifabutin, RIF = rifampin, SM = streptomycin, UL = upper lobe.

*Patient started on RFB and itraconazole, then changed to RIF and fluconazole secondary to anterior uveitis.

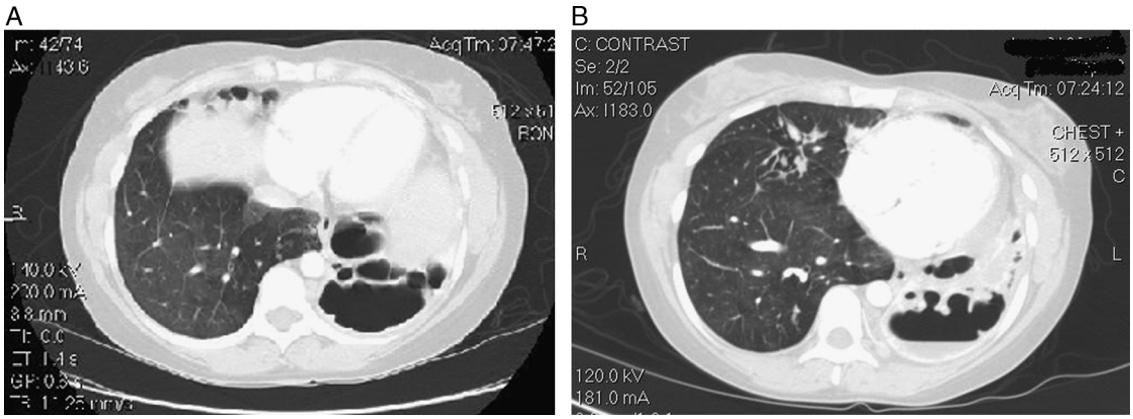

FIGURE 1. Patient 9: Computer tomography of the chest. A, Left lower lobe cavitary lesions, presumably secondary to active TB. B, Development of air-fluid levels at the time of coccidioidomycosis diagnosis. Patient had already completed TB therapy.

Of those, 35 fulfilled our inclusion criteria for further review.[3,8–10,12,15,16,18,19,27,29,33–36] Clinical characteristics of the cases are listed in Table 2.

Patients were predominantly male (25/35, 71%). The most common ethnic group was white (21/35, 60%), followed by Hispanic (6/35, 17%) and African American (4/35, 11%). Ages ranged from 3 to 62 years (median, 40 ± 15 yr).

The median age of reported patients is similar to that found in our patients, although we had more Hispanic patients, with most cases residing in south Texas or recently immigrated from Mexico. The real incidence of coccidioidomycosis in Mexico is unknown, but skin test-based epidemiologic surveys suggest that coccidioidomycosis prevalence varies between 10% and 93% in the northern states of Mexico that border the United States.[20] There is certainly a high incidence of TB in the area along the United States-Mexican border, which also corresponds to the coccidioidomycosis-endemic region.[26,28] Finally, although the risk of acquiring coccidioidomycosis seems to be the same among different races, some authors have suggested that Hispanic patients may be at higher risk for progressive or extrapulmonary coccidioidomycosis than white patients.[11,17]

Coccidioidomycosis and TB are diseases that are not often reported concomitantly. This by no means indicates a lack of association between the diseases. Although there are no prospective studies on the subject, 1 study that aimed at reporting coccidioidomycosis over a 9-year period in a predominantly Hispanic population in south Texas, found that of 41 patients with coccidioidomycosis, almost 10% also had concomitant pulmonary TB.[26] The occurrence of the coinfection has multiple common epidemiologic links, including overlapping endemic regions and similar immunologic responses required to protect the host from active disease by both pathogens.[23,31,38] Both diseases occur with increased incidence in patients receiving immunomodulatory therapies, including corticosteroids and, more recently, TNF-α antagonists.[38]

Clinical and Laboratory Features

Cotton et al[10] made an attempt to classify the coinfection based on its possible pathogenesis. However, this is difficult given the similarity in the clinical presentation of coccidioidomycosis and TB and the wide variability of clinical details provided in published reports. Nevertheless, based on case reports and authors' comments in the 35 reports in our literature review, we identified 9 cases (25.7%) in which coccidioidomycosis preceded TB, and 9 cases (25.7%) in which TB preceded coccidioidomycosis. We found 16 cases (45.7%) where the infections were diagnosed simultaneously, and 1 case (2.9%) where the infection occurred at different times in different areas of the lung (coincidental).[3,8–10,12,15,16,18,19,27,29,33–36]

Among 21 patients in the literature who had a description of the clinical features during the course of the infection, the most prevalent features were respiratory symptoms (frequently including cough and hemoptysis), chest pain (usually pleuritic), and constitutional symptoms (weakness, weight loss, and night sweats). Fever was reported in fewer than half.[3,8,9,12,16,18,19,27,29,33–36]

In our series, 6 patients had fever and most had respiratory symptoms (8/9). Hemoptysis was common (4/9), as well as weight loss (6/9) and anorexia (3/9).

Patients in previously reported series had fewer comorbid conditions than patients in the current study. In the previous reports we found only 4 cases (4/35, 11%) of diabetes mellitus, 1 case of immunosuppression in the setting of renal transplantation, 1 case of coinfection with an immunosuppressing pathogen (measles), 2 cases (2/35, 6%) of alcoholism, and 1 case of heroin use.[3,8,9,12,16,27,33,35] In our series, diabetes mellitus was diagnosed in 2/9 patients (22%), structural lung disease in 4/9 patients (44%), and alcoholism in 3/9 patients (33%).

In the cases of TB and coccidioidomycosis reported in the literature, the lungs were the most commonly compromised organs, usually with associated cavitation.[3,8–10,12,15,16,18,19,27,29,33–36] Seven of the 35 patients (20%) developed disseminated or extrapulmonary coccidioidomycosis, and 4 patients (11%) developed disseminated or extrapulmonary TB.[3,8,9,15,18] It is interesting to note that all patients with disseminated or extrapulmonary TB also had disseminated or extrapulmonary coccidioidomycosis.[8,15,16,18] There was predilection of coccidioidomycosis for bone and soft tissue (calcaneus, phalanx, humerus, femur, skull, and soft tissue adjacent to areas of bony involvement) and skin, and 3 patients had disseminated disease to multiple organs.[3,15,18]

To our knowledge, there are no previously reported cases in the literature of TB and coccidioidomycosis coinfection in the setting of HIV infection. The CDC considers disseminated or extrapulmonary coccidioidomycosis an AIDS-defining condition, while both pulmonary and extrapulmonary TB qualify.[4] In the current series, the patient with AIDS, pulmonary TB, and TB lymphadenitis developed fatal disseminated coccidioidomycosis, including pulmonary and meningeal involvement despite therapy with appropriate TB agents, antiretroviral therapy (nelfinavir, zidovudine, and lamivudine), and high-dose fluconazole.

An important number of patients with HIV living in endemic regions may be at risk for progressive pulmonary

TABLE 2. Characteristics of Patients With TB and Coccidioidomycosis Coinfection, Previous Reports

Ref./Year	No. of Cases	Clinical Presentation and Laboratory Features	Radiologic Findings	Treatment and Outcome
3/2002	2 Cases	Case 1. 17 y/o Hispanic F with cough with purulent sputum, weight loss, fevers that started 1 mo after delivery. She also had esophageal candidiasis but HIV was negative. Had positive sputum cultures for TB. Was started on antitubercular therapy but developed verrucous skin lesions and inflammatory arthritis of L elbow. Joint aspiration was positive for CM on smear and cultures.	Case 1. Bilateral UL infiltrates with cavitation. Later, after 2 mo of TB therapy, osteolytic lesions on phalanx and L humerus.	Case 1. Managed with antitubercular therapy as well as amphotericin B followed by itraconazole.
		Case 2. 42 y/o M with IVDU, alcoholism, and smoking history admitted with 4 mo of fever, diaphoresis, and cough with purulent sputum, weight loss, and dysphagia. He was malnourished and had LUL cavity. Had negative HIV and positive sputum for CM and TB.	Case 2. RUL destruction and confluent cavities, with bronchogenic spread on the L.	Case 2. Discharged on itraconazole and antitubercular therapy.
8/1981	2 Cases	Case 1. 56 y/o M on hemodialysis for 2 mo received a renal transplant and was immunosuppressed with azathioprine, radiotherapy, and methylprednisolone. After graft failure and nephrectomy, patient developed infiltrate and had AFB on bronchoscopy and positive CM on sputum. CF became positive. Autopsy with positive pulmonary CM and TB.	Case 1. LLL infiltrate with some surrounding nodules.	Case 1. Dead despite RIF, INH, EMB.
		Case 2. 53 y/o F with DM on hemodialysis presented with fever, diarrhea, weight loss, and neck nodules. Positive urine cultures and CF for CM. Aspirate of lymph node grew AFB. Autopsy with only pulmonary CM and TB, as well as *C. immitis* on thoracic lymph node tissue.	Case 2. Bilateral reticulonodular infiltrates.	Case 2. Dead from bleeding after attempt to obtain IV access. Received INH, RIF, and EMB.
9/1952	3 Pediatric cases. Only 1 with CM diagnosed by cultures.	Case 1. 3 y/o Mexican M, father with TB, initially treated for influenza meningitis and otitis and re-admitted with croupy cough and vomiting followed by seizures. PPD and coccidioidin were positive. Gastric aspirate was positive for TB. Later developed forehead abscess that had positive cultures for CM.	Progressive L apical infiltrate along the cardiac border with cavitations along the RUL and RML, with additional lesions on skull.	Developed measles and varicella sequentially. Treated with SM and stilbamidine. Patient died.
10/1954	24 Cases, 9 with microbiologic/ histopathologic diagnosis	7 Cases treated with surgical intervention, 2 with observation. Ages from 13 to 62 y/o, 4 M, 8 white, 1 Hispanic. Three diagnosed with CM based on histopathology, 1 on histopathology and culture, and 5 based on sputum culture. Eight diagnosed with TB by sputum examination (1 with empyema) and 1 by gastric washing.	Described in 3 cases: Case 1 started with R hilar cavity from CM, followed by extension to LUL when TB was diagnosed. Case 2: LLL field infiltrate, followed by R empyema. Case 3: Extensive lung parenchymal destruction.	Most common intervention was pulmonary resection. Five treated with pneumothorax; all 7 patients treated with surgery recovered completely. Two patients were referred to a sanatorium on observation.
12/1960	1 Case	37 y/o White M smoker presented with persistent cough. Positive resected UL for granulomas and TB and CM on cultures.	LUL mass.	Resolved after surgery and "antimicrobial therapy."
15/1949	1 Case	34 y/o White M smoker with persistent cough, malnutrition, and skin lesions. Initial improvement followed by increased number of skin lesions and positive cultures for CM and TB in lung and extrapulmonary sites. CM meningitis.	1 cm Infiltrate on the 1st intercostal space, progressed to miliary pattern.	Dead despite SM and vitamin D therapy and potassium iodide.

16/1951	1 Case	52 y/o M initially admitted with abnormal CXR for treatment of tuberculosis, followed by progressive weight loss. Patient then developed R foot erythema, edema, and pain on foot, with a draining sinus. 6 mo later, developed similar lesion on L foot. Wound cultures were positive for TB. Biopsy and debridement of lesions performed and were positive for CM on smear and cultures. Positive CF for CM.	R calcaneus bone with multiple cysts and limited periosteal reaction, with sinus formation. Two mo later, distal tibia with marginal erosion, abscess, and sinus formation, as well as soft tissue edema.	Treated with surgery and SM. Clinical improvement with occasional drainage from primary lesion and a self-limited proximal femoral lesion that was not biopsied.
18/1949	1 Case	21 y/o M presented with asthenia, malaise, and nonproductive cough. Initial improvement followed by formation of sternal mass, headaches, and scalp nodules. Progressive disease with multiple lesions, bone lesion on humerus. Necropsy with TB and CM on lung and disseminated CM including meningitis. Gastric aspirate positive AFB. Foot abscess: CM.	L side effusion and R apical infiltrate. Humerus X-ray with bone destruction.	Penicillin, sulfas. Patient died.
19/1950	1 Case	52 y/o Filipino with cough and purulent sputum, fever. Positive TB cultures of sputum and positive sputum culture and CF for CM.	Density on RLL.	No treatment. Clinical improvement.
27/1960	1 Case	22 y/o White M with UL fibrosis on X rays. Underwent R upper pulmonary segment resection. Sample was positive for CM and TB on cultures.	R apex with fibrosis, calcification, and other softer-appearance areas.	Treated with PAS and SM after lung resection. Asymptomatic at 9 mo.
29/1947	1 Case	27 y/o M presented with dyspnea, L-sided pleuritic chest pain, fever, and fatigue.	R lung collapse with hydropneumothorax. CM and TB recovered from pleural fluid.	Observation, clinical improvement.
33/1953	6 Cases	Case 1. 34 y/o African-American M with pulmonary TB with consolidation (positive sputum AFB) managed with SM followed by PAS. Patient died and was found to have CM spherules on multiple organs on autopsy.	Case 1. Bilateral pulmonary infiltrates with spread of disease.	Case 1. SM and PAS used sequentially produced transient improvement. Then patient developed appendicitis and sepsis. Patient died.
		Case 2. 26 y/o African-American M admitted with dry cough and pleuritic chest pain, night sweats, fatigue x 4 mo, hemoptysis x 2 wk. Positive sputum cultures for AFB negative smears. Sputum cultures positive for CM. Improved without therapy.	Case 2. Infiltrate and cavity on LUL.	Case 2. Improvement with bed rest.
		Case 3. 56 y/o white M with DM. Initially positive sputum cultures for CM, later pulmonary cavity progressed and developed air-fluid level and patient had positive AFB and cultures for TB on sputum. He was treated with PAS and SM with transient improvement but later recurrence.	Case 3. Coin lesion on RUL, that progressed with time to cavity with air-fluid level.	Case 3. Transient improvement, refused surgery.
		Case 4.35 y/o white M, with history of TB contacts, presented with cough, weight loss, dyspnea. Had positive sputum cultures for CM followed by positive TB sputum cultures. Treated With SM and PAS.	Case 4: Bilateral UL infiltrates with cavitations.	Case 4. Negative cultures with pneumoperitoneum and PAS + SM. Cultures became negative.
		Case 5. 51 y/o white F with history of pleural effusion 25 yr before, presented with upper respiratory symptoms, RUL cavity. Sputum cultures were positive for CM. Later developed R middle lung infiltrate and positive AFB sputum cultures.	Case 5. RUL cavitary lesion and infiltrates. Improved initially and followed by development of RML field infiltrate.	Case 5. Improvement with bed rest only.

(continued on next page)

TABLE 2. Characteristics of Patients With TB and Coccidioidomycosis Coinfection, Previous Reports

Ref./Year	No. of Cases	Clinical Presentation and Laboratory Features	Radiologic Findings	Treatment and Outcome
		Case 6. 39 y/o white M presented with LUL infiltrate and positive skin test for CM and TB, with negative sputum cultures. Later, patient developed upper respiratory symptoms fevers and was found to have diffuse L lung infiltrates. Sputum was positive for AFB and CM. He was started on PAS and SM and LUL resection that disclosed granulomas and AFB. Cultures were positive for both TB and CM.	Case 6. Initially coin lesion on LUL, followed by cavitation and some regression after therapy, before resection.	Case 6. Treated with PAS and SM as well as LUL resection. Asymptomatic with negative cultures.
34/1948	1 Case	24 y/o African-American M with history of pulmonary TB admitted with intermittent anterior chest pain. Initially diagnosed with TB and later developed worsening X-rays, positive CM cultures on sputum, positive CF for CM, and persistent positive AFB on sputum.	Bilateral UL infiltrates. Later, R apical thin-walled cavity and LUL progressive infiltrates.	No treatment. Patient had worsening clinical condition and left against medical advice.
35/1974	6 Cases, 2 cases with radiologic and clinical features.	Ages 44 to 62 y/o. 4/6 with positive CF for CM and 5/6 with positive sputum cultures. Only 2 cases described in detail.	Case 1. Cavitary lesion on LUL, approximately 4 cm in diameter, with multiple small cavities below it.	Case 1. Treated with surgery and EMB, INH, SM, PAS (later substituted for RIF), and amphotericin B.
		Case 1. 57 y/o Indian F with DM and previous TB at age 7 yr, presented with LUL cavity and positive sputum AFB. LUL resection disclosed granulomas and CM spherules.	Case 2. Bilateral cavitations.	Case 2. Improvement of TB with negative cultures. Persistent CM on sputum cultures. Amphotericin B for CM. Radiologic improvement.
		Case 2. 53 y/o white M with history of alcoholism and heavy smoking admitted due to abnormal-rays, treated with SM, EMB, and INH. Sputum sent for culture due to persistent AFB and was positive for CM and negative for TB.		
36/1966	1 Case	45 y/o White M with weakness, anorexia, weight loss, cough with white sputum. Initially negative AFB, discharged but exposed to TB in hospital, later readmitted with weakness, weight loss, and found to have positive sputum stains and cultures for TB. LUL resection with positive stains and cultures for CM.	RUL with 2 cm cavity, later multiple LUL cavities.	RUL improved on antitubercular therapy (not defined). Clinical improvement.

Abbreviations: See previous table. AFB = acid-fast bacilli, IVDU = intravenous drug use, SM = streptomycin.

or disseminated coccidioidomycosis. The CD4 count at the time of coccidioidomycosis disease in HIV patients[1] is usually <250 cells/mm^3. On the other hand, TB can occur at any CD4 count, and it can accelerate the decline in CD4 cells in patients with HIV. Due to the low and declining incidence of TB in the United States, HIV TB is more commonly reported in HIV-positive persons with very low CD4 lymphocyte counts.[5,23] The reason for the lack of reports of coccidioidomycosis and TB coinfection in the setting of AIDS is not clear.[1]

Coccidioidomycosis was consistently diagnosed by sputum cultures. Of 17 patients with complement fixation results reported, 8 (47%) were positive on initial testing, 5 (24%) were initially negative but became positive, and 2 (12%) remained negative. In the remaining 2 cases, the authors did not record the date or time of initial testing.[8,9,10,19,29,34,35]

Serologic testing was commonly reported in older series, and complement fixation may be helpful in the diagnosis and follow-up of patients with coccidioidomycosis. However, given multiple testing protocols, it is difficult to compare titers obtained at different centers. Furthermore, the sensitivity of complement fixation alone may be as low as 56%, particularly among immunosuppressed patients.[30]

Nineteen patients had purified protein derivative (PPD) testing done. Of these, 15 patients (79%) were reported positive. However, PPD testing materials and methods were not consistently documented.[8,9,15,18,19,27,29,33–36]

In our series we observed that the coinfection was more common among patients who failed to improve despite effective antitubercular therapy. It is interesting to note that clinically, the 2 diseases may be indistinguishable, and it may be prudent to always consider the coinfection among patients coming from coccidioidomycosis-endemic regions. There are some clinical features that may suggest the presence of the coinfection, but all patients from endemic regions should be considered at risk (Table 3).

Radiologic Features

Patients presenting with pulmonary coccidioidomycosis or TB monoinfection may have similar radiologic features. TB disease can often be divided into primary disease (focal infiltrates, often in the lower lobes, occasionally associated with ipsilateral hilar or paratracheal lymphadenopathy and less commonly, miliary infiltrates) or postprimary disease (dense infiltrates in the apical, posterior segments of the upper lobes and cavities with thick, irregular walls).[2]

Primary coccidioidomycosis presents as a unilateral, mass-like consolidation, associated with lymphadenopathy in about 20% of cases. Some cases evolve into chronic progressive coccidioidomycosis, characterized by bilateral infiltrates, nodular with cavitation, and others into a nodule or a mass-like coccidioidoma. Some other patients develop upper lobe thin-walled cavities of variable size.[32] Rarely, patients develop disseminated disease with a miliary distribution and mediastinal lymphadenopathy.[2]

Radiologic features reported in the literature in the setting of TB and coccidioidomycosis coinfection were diverse (see Table 2). They varied depending on the age of the patient and the stage of the disease (with the tendency to develop cavitation as the disease evolved, commonly encountered in TB monoinfection). Most patients eventually developed cavitary disease, most commonly involving the upper lobes. In other patients, especially those with disseminated disease, a miliary pattern was noted.

TABLE 3. History, Clinical, and Laboratory Clues Suggesting Coinfection With Coccidioidomycosis in Patients With TB

Epidemiologic factors
Patient resides in a coccidioidomycosis-endemic region.
Patient has history of residing in or traveling through a coccidioidomycosis-endemic region.
Clinical features
Persistent symptoms despite TB therapy.
Progressive disease despite culture-directed TB therapy.
New air-fluid levels in pre-existing pulmonary cavities without evidence of recurrent TB.
Disseminated granulomatous disease with multifocal skeletal involvement.
Laboratory features
Positive sputum cultures for *C immitis.*
Positive coccidioidomycosis IgM serology: CF, immunodiffusion, or ELISA.

Abbreviations: See previous tables.

Therapeutic Implications and Clinical Outcomes

Previous series in the literature were limited by the small number of patients and by the lack of safe and effective therapy. In the pre-antibiotic era, many patients with pulmonary TB would experience disease remissions and exacerbations, occasionally helped by supportive care under the sanatorium model. Many cases of coccidioidomycosis would have been self limited and eventually resolve without specific therapy. In the current series, we observed a favorable response to concomitant TB and coccidioidomycosis therapy in our 9 patients, except for the fatal outcome of disseminated coccidioidomycosis in the setting of AIDS. As with our patient who received less than 2 weeks of triazole therapy before death, patients who complete at least 2 months of antifungal therapy have the best outcomes.

Medical therapy of coccidioidomycosis can be complicated by the drug interactions between triazole antifungal agents and TB medications. Rifampin induces CYP450 (CYP3A4) in the liver and intestine, which may decrease the area under the curve (AUC) of itraconazole by 80%–90% and the AUC of fluconazole by 23%.[24] The concomitant use of itraconazole and rifampin is not recommended. Patients treated with fluconazole for severe coccidioidomycosis (such as meningitis) may have better outcomes when higher doses are used, and rifampin should, again, be used with caution in this setting.[24,39]

Diagnostic and pharmacologic advances for the diagnosis and treatment of coccidioidomycosis and TB make it easier to both diagnose and treat coinfection. The clinician should consider both diseases in the differential diagnosis of a patient with these demographic and geographic risk factors.[23,31] It is not clear whether all coinfected patients need antifungal therapy in addition to their TB regimen. Many *Coccidioides immitis* infections are self limited, and most previously reported cases were described before current triazole antifungal agents became available.[8–10,12,15,18,19,22,27,29,33–36] However, there may be certain clinical settings in which concurrent TB and antifungal therapy is warranted.[3,8,17]

The current case series has limited applicability to clinical practice. First, this was a retrospective study and the data were obtained at a TB referral hospital. Second, due to limited patient numbers, we cannot comment on whether coinfection adversely affected patient outcomes. In addition, it is likely that some patients may develop undetected and self-limited pulmonary coccidioidomycosis during management for active TB.[14,37]

In conclusion, TB and coccidioidomycosis can coexist in the same host, as they share geographic endemicity as well as significant predisposing conditions (such as HIV infection). The

rare but significant co-occurrence of TB and coccidioidomycosis illustrates the need to obtain a detailed epidemiologic history for patients diagnosed with TB. TB with coccidioidomycosis coinfection is often indistinguishable from TB alone, but can manifest as relapsing pulmonary or extrapulmonary symptoms in the setting of seemingly adequate therapy for TB. Both diseases may have a fulminant course in immunosuppressed individuals. Patients in endemic areas should be evaluated for the potential of coinfection and treated when clinically indicated.

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