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Original contribution

Cavitary pulmonary coccidioidomycosis: pathologic and clinical correlates of disease☆,☆☆

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Summary Cavitary pulmonary coccidioidomycosis is a difficult diagnosis to establish due to the poor sensitivity of serological tests and rarity of culture from sputum. A pathologic and clinical analysis was performed of 21 consecutive patients with surgically resected cavities that proved to be coccidioidomycosis. Ten patients (48%) had serological evidence of *Coccidioides* infection, and 1 patient cultured *Coccidioides* spp. from sputum. The definitive diagnosis of coccidioidomycosis was made in the remaining 10 patients (48%) upon microscopic examination of tissue. The pleura showed fibrous pleuritis in 7 patients (33%) and eosinophilic pleuritis in 4 cases (19%); granulomas without microorganisms were demonstrated in 4 cases (19%). The cavity wall showed chronic inflammation and occasional giant cells but no granulomas and no microorganisms. The cavity contents included a mycetoma in 6 cases (28%); the cavity lining showed neutrophils and caseous necrosis; *Coccidioides* hyphae were present in 13 (62%) and spherules in 16 (76%) cases but often were rare. Adjacent lung showed lymphoid hyperplasia with chronic bronchiolitis in all cases; satellite granulomas with diagnostic spherules were variably present. The histopathology of cavitary coccidioidomycosis is strikingly variable depending on what area is sampled by biopsy, and microorganisms may be rare. This may explain the high rate of failure of diagnosis by fine needle aspiration and bronchoalveolar lavage. Pathologists in nonendemic areas must be aware of these findings, as this disease is now diagnosed worldwide.
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1. Introduction

Coccidioidomycosis is an infection with 1 of 2 closely related species of soil fungi, *Coccidioides immitis* and *Coccidioides posadasii*. After inhalation of the fungus, patients may experience pulmonary symptoms and a localized pneumonia detectable on chest imaging. Coccidioidomycosis produces a wide range of host responses in the lung, from well- to poorly formed granulomas, enlarging caseous nodules, eosinophilic infiltrates, and acute inflammation resembling bacterial pneumonia. The microorganism in tissue may exist in spherule or hyphal form or both. The spherule is virtually pathognomonic for *Coccidioides* spp., whereas *Coccidioides* hyphae may resemble other fungal hyphae of similar size, such as *Aspergillus* spp. It is estimated that as many as 13% to 15% of patients with pulmonary coccidioidomycosis on chest imaging will form a

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pulmonary cavity [1]. Cavitary pulmonary coccidioidomycosis is one of the most difficult presentations of coccidioidomycosis to diagnose because sputum cultures are often negative and serologies have a low sensitivity. Furthermore, the pathologic findings in tissue specimens are not always diagnostic, and the range of histologic changes is not generally appreciated.

Cavitary lung disease in coccidioidomycosis sometimes leads to surgical resection. The histology of such surgical pathology specimens has been described in several series, but not in detail [2-5]. Consequently, we reviewed a series of resected cases of cavitary pulmonary coccidioidomycosis, noting the clinical characteristics of the patients, as well as analysis of the microscopic pathology to include estimating the abundance of microorganisms and the histologic response by the host to the microorganism. More specific knowledge of the histology of cavitary coccidioidomycosis will allow for more precise interpretation of cytologic core or fine needle aspiration biopsies of such lesions [6-9].

2. Materials and methods

2.1. Clinical evaluation

Twenty-one consecutive patients with a *Coccidioides* spp. cavitary lesion of the lung excised by thoracotomy from January 2008 to October 2011 were studied. This occurred at the main teaching hospital of the University of Arizona, University of Arizona Medical Center. The study was approved by the Investigational Review Board of the University of Arizona, and patient consent was waived. Pertinent clinical data were extracted from patient records. Outpatient notes, inpatient surgical notes, radiology reports, laboratory data, and pathology reports were all reviewed. The following clinical aspects were identified and analyzed: patient demographic data including sex, age, nationality and living condition, comorbid conditions, smoking, immunosuppression, and reason for surgery. In addition, the following was obtained on each patient: *Coccidioides* serological results, cavity location and size on chest imaging, and whether a fungal ball was present or satellite granulomas identified on chest imaging.

2.2. Pathologic evaluation

The computerized database of surgical pathology specimens was searched for cases of resected cavitary coccidioidomycosis for the same period (2008 and 2011). The pathology was reviewed according to the following scheme, with each specific feature being semiquantitatively graded as 0, absent; 1+, occasional; 2+, frequent; 3+, abundant. The pleura was evaluated for fibrin, neutrophils, granulomas, organization, fibrosis and chronic inflammation, fungal organisms, and evidence of rupture. The cavity wall was evaluated for re-epithelialization, palisading histiocytes, granulomas, giant cells, and chronic inflammation with fibrosis. The cavity itself was evaluated for fungus ball, caseation, neutrophilic infiltrate, hemorrhage, and the presence of *Coccidioides* microorganisms (noting their abundance and whether they were in the form of spherules, hyphae, or both). The lung adjacent to the cavity was evaluated for granulomas (necrotizing or nonnecrotizing), eosinophilia, organizing pneumonia, alveolar macrophages, chronic bronchiolitis, vascular inflammation, and lymphoid hyperplasia. We also noted if any lymph nodes were examined with the specimen and whether these contained granulomas and microorganisms. The number of hematoxylin and eosin (H&E)–stained microscopic slides and slides with fungal stains (Grocott's methenamine silver [GMS]) per case was tallied.

3. Results

3.1. Clinical evaluation

Twenty-one patients who underwent surgical removal of a coccidioidal cavity were included in the study. Eleven patients (52%) had a prior diagnosis of *Coccidioides* infection, and of those, 6 (28%) were receiving therapy at the time of surgical resection. Three of the patients had never received therapy for coccidioidomycosis. The definitive diagnosis of coccidioidomycosis as the cause for the lung cavity was established by pathologic evaluation of resected lung tissue in 10 patients (48%).

The patients ranged in age from 13 to 77 years (Table). Twelve patients were women and 9 were men. Putative risk factors for cavity formation included 7 patients (33%) with diabetes and 11 patients (52%) with a history of smoking; 4 patients were immunosuppressed: 1 patient with HIV, 1 with active rectal carcinoma, 1 patient with rheumatoid arthritis receiving a disease-modifying antirheumatic drug, and 1 patient with autoimmune hepatitis who was receiving steroids and azothioprine.

Symptoms included chest pain in 6 patients (28%), cough in 16 (76%), shortness of breath in 13 (62%), fever in 5 (24%), hemoptysis in 10 patients (48%), and 2 patients (10%) complained of weight loss. The reason for surgery (Table) included 7 patients (33%) with continuing hemoptysis, 7 patients (33%) with an enlarging cavity, 3 patients (14%) whose cavity ruptured into the pleural space, and 3 (14%) patients with continuing symptoms.

Eleven patients (52%) had eosinophilia in the peripheral blood (>5% eosinophils) (Table). All of the patients underwent bronchoalveolar lavage, and on only 1 occasion was *Coccidioides* grown from specimens obtained by this procedure. Ten patients (48%) had positive serological results, and there appeared to be no relationship to between serological titers and the size of the cavity. Cavities on

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