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Original contribution

Surgical pathology of pleural coccidioidomycosis: a clinicopathological study of 36 cases☆,☆☆

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Summary Most pulmonary coccidioidal infections are intraparenchymal; the pleurae are rarely involved. Pleuritis is a recognized complication of ruptured cavitary infections and occasionally occurs in other settings but has not been fully characterized. To define the clinical and histopathologic characteristics of pleural coccidioidomycosis as encountered by surgical pathologists, we reviewed the clinical history, imaging, and histology of 36 biopsy-, resection-, or autopsy-confirmed cases (with coccidioidal spherules present in pleural tissue; median age, 39 years; 22 men). These represented 7% of all pulmonary coccidioidal infections and showed 2 modes of presentation, including ruptured cavitary infection (26) and pleural-predominant disease with milder parenchymal involvement (10). Risk factors included immunodeficiency, smoking, and occupational exposure to soil. Common symptoms (median, 5 weeks) included cough (47%), chest pain (44%), and dyspnea (39%). Imaging often showed pleural adhesions (64%) and effusions (61%). Treatment included lobectomy or decortication, with antifungal medications. All cases showed granulomatous pleuritis. Both modes of presentation showed similar histologic features, including the composition of inflammatory infiltrates, degree of fibrosis, and extent of necrosis. Spherules were usually few (mean density, <1/10 high-power field). Three deaths occurred (all with ruptured cavities); the remaining patients recovered. Differential diagnosis of pleural effusions should include coccidioidomycosis, particularly in endemic areas, even without significant intrapulmonary disease. Most cases of coccidioidomycotic pleuritis are encountered by pathologists after resection of ruptured cavities with decortication, but pleural-predominant infections may be biopsied for diagnostic purposes. Spherules are usually rare in pleural tissue, and liberal sampling, cultures, or serologic studies may be required to confirm the diagnosis.

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1. Introduction

Coccidioidomycosis is an infection caused by the pathogenic soil-dwelling, thermally dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii* and is endemic to the southwestern United States, especially Arizona and southern California, although this endemic area also extends into the arid regions of Nevada, Utah, and western Texas, as well as northwestern Mexico [1–6]. Infection almost always involves the lungs and is subclinical in about 60% of patients. When infections are clinically apparent, they are usually mild and self-limited.

Complications of pulmonary coccidioidomycosis are uncommon but occur more often in immunocompromised patients and some ethnic groups [4,7]. Sequelae of chronic pulmonary infections include formation of pulmonary nodules or peripheral thin-walled cavities [8], and up to 15% of patients will also develop pleural effusions [6,9,10]. Most of these are sterile parapneumonic effusions that do not require surgical intervention [10]; however, in unusual cases, the pleurae can become infected, and empyema is a recognized complication of ruptured cavities or in the setting of disseminated infection [11]. In exceptional cases, primary pleural infection has been reported in the absence of significant parenchymal disease [12–14].

Because of its rarity, pleural coccidioidomycosis may not be considered in the differential diagnosis of pleural effusions, even in endemic areas, and its recognition requires a high index of clinical suspicion, combined with imaging and laboratory studies. Serologic studies remain a mainstay of clinical evaluation and are very sensitive and specific; pleural fluid analysis, fungal cultures, and molecular assays are helpful if positive but are less sensitive [15]. Even in a patient with positive serologic testing, pleural biopsies may be undertaken to confirm the diagnosis and to exclude malignancy or other processes. Despite recognition for many decades that *Coccidioides* can infect the pleurae, pleural coccidioidomycosis remains incompletely understood and its histopathologic features have not been systematically evaluated. Consequently, we reviewed a series of cases of pleural coccidioidomycosis, to define the clinical and histomorphologic characteristics of this condition. We used a narrow case selection process, including only those cases diagnosed on a surgical biopsy, surgical resection, or autopsy, to reflect those cases that are most likely to be encountered by a surgical pathologist.

2. Materials and methods

This study was approved by the respective institutional review boards. All cases of surgically biopsied, surgically resected, or autopsy-confirmed pleural coccidioidomycosis during a 13-year period (2000-2012) were identified by searching the surgical pathology databases at the University of Arizona and Mayo Clinic in Arizona. Search terms included "pleura" or "pleuritis," cross-referenced with "*Coccidioides*," "coccidioidomycosis," "coccidioidal," or common misspellings of these terms. To determine the frequency of this diagnosis relative to the total number of histologically confirmed coccidioidal infections (at any anatomical site), a parallel search of the surgical pathology database was performed using only the above set of terms for the organisms. To determine the frequency of this diagnosis relative to the total number of cases involving the lungs, a similar search was performed and cross-referenced with the terms "lung" or "lobe."

For inclusion in the study, the presence of coccidioidal spherules within pleural tissue or the overlying fibrinous exudate was required; cases of pleuritis without spherules were presumed to represent pleuritic reactions in the setting of an underlying parenchymal infection, and not true infectious pleuritis, and were excluded from further review. Using these criteria ensured inclusion of only those cases with true infection of the pleura by the organisms, while simultaneously ensuring inclusion of all potential histologic variants.

After cases of pleural coccidioidomycosis were identified, clinical history was reviewed including available clinical notes, imaging reports, surgical reports, and laboratory studies. Pertinent clinical information was recorded, including patient age, sex, race, and medical history, with particular attention given to underlying pulmonary disease, previous infections with *Coccidioides*, and evidence of immunodeficiency, including primary causes (eg, diabetes mellitus or autoimmune disease) and iatrogenic causes (eg, previous organ transplantation or immunosuppressive medications). Pertinent social elements were also recorded, including occupational history and history of tobacco smoking. Symptoms were reviewed in detail. Thoracic roentgenographic and computed tomographic (CT) imaging studies were reviewed, and pertinent radiologic features were tabulated, including the laterality of disease, presence of cavitary masses, parenchymal infiltrates or nodules, parenchymal consolidation, pleural adhesions, effusions, pneumothorax, and pleural thickening. Results of available laboratory studies were tabulated, including diagnostic serology, microbiologic cultures, and molecular testing. Pertinent aspects of the hospital course were detailed, including operations performed and antibiotic medication(s) used, and the functional status was recorded at the time of most recent follow-up.

Histologic slides of surgically resected pleural tissue were retrieved from the pathology archives of each institution and reviewed in detail by 2 authors (B.T.L. and R.W.R.). The number of slides evaluated was tallied. Original diagnoses were confirmed on sections stained with hematoxylin and eosin and on additional sections stained with Gomori methenamine silver (GMS) when available.

To characterize inflammatory infiltrates, the presence of neutrophils, lymphocytes, plasma cells, eosinophils, giant