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Case Report

Unique presentation of an endemic opportunistic fungal infection: Disseminated coccidioidomycosis mimicking metastatic lung cancer with endotracheal and endobronchial involvement

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ABSTRACT

Coccidioidomycosis is a fungal infection primarily Endemic in the Southwest United States. Disseminated Coccidioidomycosis is a life-threatening variant that mainly occurs in an immunocompromised host. This report describes an unusual presentation of disseminated Coccidioidomycosis in an immunocompetent individual. The patient was admitted with a subacute cough, progressively worsening shortness of breath, significant weight loss, nodular skin lesions in upper extremities, and acute hypoxemic respiratory failure. Chest imaging revealed extensive nodularity and mass-like lesions. What sets this case apart is the significant endotracheal and endobronchial involvement, which mimicked metastatic lung cancer. The diagnosis was confirmed through serology and bronchoscopy biopsy. This case underscores the critical importance of considering detailed travel history and maintaining a high index of suspicion for fungal infections in patients with endobronchial lesions, particularly in regions where Coccidioidomycosis is endemic.

1. Introduction

Coccidioidomycosis is a systemic fungal infection caused by Coccidioides species [1]. It commonly affects individuals living in or traveling to endemic areas, such as Arizona, California, New Mexico, and Texas [2–5]. Disseminated coccidioidomycosis is an uncommon (1%) but life-threatening form of the disease, with most reported cases found to be immunocompromised patients [5]. The clinical manifestations of disseminated coccidioidomycosis can vary widely, often resembling other infectious or neoplastic processes. Early and accurate diagnosis is crucial for appropriate management, as delayed recognition can lead to disease progression and poorer outcomes. The presented case depicts an unusual presentation of disseminated coccidioidomycosis mimicking metastatic lung cancer with endotracheal and endobronchial involvement in an immunocompetent patient.

2. Case presentation

An 80-year-old immunocompetent African-American man presented with progressively worsening dyspnea, productive cough, nocturnal sweating, anorexia, and three-month weight loss after returning from a month-long stay in Arizona. He noted that approxi-

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mately 6 months before admission, he had a COVID-19 infection that did not require hospitalization. Immediately before hospital admission, he received a 10-day course of Azithromycin followed by a 7-day course of Levofloxacin with no notable improvement.

On arrival, the patient exhibited signs of acute hypoxemic respiratory failure with an oxygen saturation of 85% on room air. He required supplemental oxygen via nasal cannula, administered at a flow rate of 5 L per minute, which improved his saturation to 94%. Vital signs were notable for a heart rate of 110 beats per minute, a respiratory rate of 27 breaths per minute, a blood pressure of 102/85 mmHg, and a temperature of 37.2 °C. Physical examination revealed bilateral basal crackles on auscultation of the lungs, yet no wheezing or use of accessory muscles was noted. The cardiovascular examination was unremarkable, with no murmur or peripheral edema or distended neck veins. Abdominal examination was normal with no hepatosplenomegaly or tenderness. His skin was warm and dry, without cyanosis or clubbing. However, nodular lesions noted in the upper extremities (Fig. 1). Neurologically, he was alert and oriented, with no focal deficits. Laboratory work up are shown in Table 1.

A chest computed tomography (CT) scan demonstrated extensive bilateral nodules exhibiting a miliary pattern and the presence of a moderate-sized pleural effusion on the right side. Additionally, multiple enlarged mediastinal lymph nodes were observed, as depicted in Fig. 2. The thoracentesis procedure yielded pleural fluid that was subsequently analyzed. The protein level in the pleural fluid was 5.8 g/dL, compared to the serum protein level of 8.2 g/dL. This results in a pleural fluid to serum protein ratio of 0.71. Additionally, the lactate dehydrogenase (LDH) level in the pleural fluid was measured at 179 U/L, while the serum LDH level was 391 U/L, leading to a pleural fluid to serum LDH ratio of 0.46. Based on these findings, particularly the total protein ratio, the pleural fluid is consistent with an exudate as defined by Light's criteria. For a comprehensive overview of the pleural fluid analysis, please refer to Table 2.

Subsequently, a flexible bronchoscopy was conducted, revealing the presence of multiple nodules/masses in the endotracheal and endobronchial regions (Fig. 3). Bronchoalveolar lavage specimens from the right middle lobe, as well as pooled bronchial washing specimens, were sent for Gram staining, along with bacterial and mycobacterial cultures, all of which were unrevealing. However, microscopic examination of endotracheal biopsy specimens, with special fungal stains from the right mainstem bronchus and trachea, confirmed the presence of Coccidioides spherules, indicative of coccidioidomycosis. This diagnosis was further supported by obtaining tissue biopsy specimens from the lesion in the skin of the left hand, which also demonstrated the presence of Coccidioides spherules (Fig. 4).

Coccidioides antibodies tested positive for IgM and IgG by immunodiffusion with a high Complement Fixation-Antibody (CF-Ab) titer exceeding 1:1024 (Performed by Quest Diagnostics Nichols Laboratory). After being diagnosed with coccidioidomycosis, the pa-

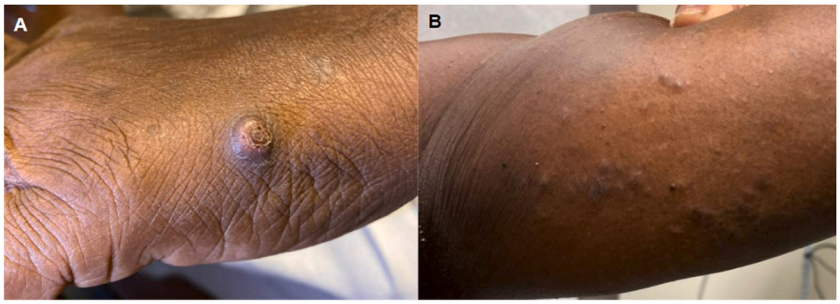

Fig. 1. Skin lesions; (A) Ulcerated nodular lesion in the left hand; (B) Right arm nodular lesions.

Table 1
Laboratory workup. Abnormal values. (L): Low, (H): High.

Laboratory marker	Patient's values	Normal/Reference Range
Complete Blood Cell with differential		
WBC	56.5 (H)	3.8–10.8 K/uL
RBC	3.18 (L)	4.18–5.22 M/uL
Hemoglobin	8.7 (L)	12.0–16.0 g/dL
Hematocrit	27.0 (L)	36.0–48.0 %
Platelet Count	330.0	150–450 K/uL
IANC	38.4 (H)	1.9–10.8 K/uL
Neutrophils %	67.9	51.0–89.0 %
Lymphocytes %	2.7 (L)	10.0–40.0 %
Eosinophil %	4.3	0.0–10.0 %
Basophil %	1.2	0.0–3.0 %
Immature Granulocyte %	0.1 (H)	0.0–1.0 %
Other inflammatory/serology markers		
C-Reactive Protein (CRP), Blood	16.1 mg/dL	< 1 mg/dL
Lactate Dehydrogenase (LDH), Blood	391 U/L	140–271 U/L
Procalcitonin	0.08 ng/mL	< 0.499 ng/dL
ANA Screen, Blood	< 1:40	< 1:40

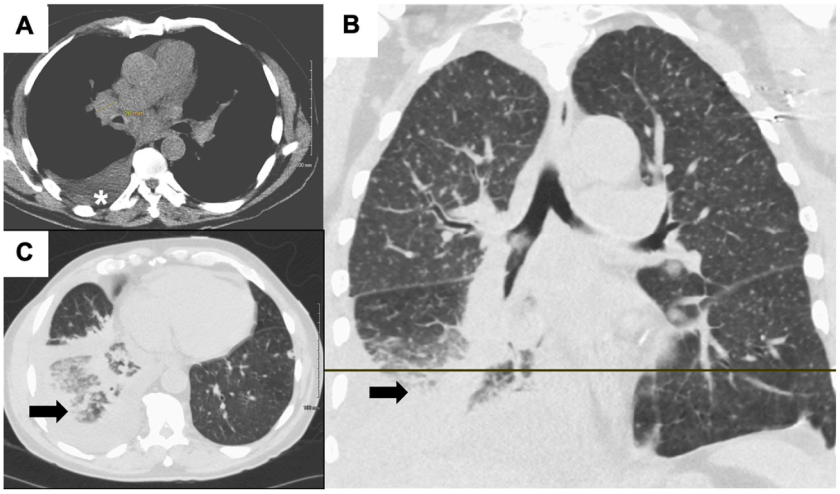

Fig. 2. Chest CT scan Without Contrast on Admission. (A) Axial CT image (Soft-tissue window) showing a right pleural effusion, marked with an asterisk (*). (B) Coronal CT section (Lung window) demonstrates diffuse micronodular opacities bilaterally along with consolidation in the right lower lobe (Black arrow). A black horizontal line indicates the cut level depicted in Image (C) corresponding to the Axial view (Lung window), highlighting the consolidation process surrounding atelectatic lung (Black arrow).

Table 2
Pleural fluid studies. Abnormal values: (L): Low, (H): High.

Pleural Fluid Analysis	Patient values	Reference Range & Units
Body Fluid Appearance	Hazy	Clear
Basophils, Body Fluid	0	%
Body Fluid Color	Yellow	Colorless, Gray
Neutrophils, Body Fluid	42	%
Eosinophils, Body Fluid	0	%
Lymphocytes, Body Fluid	37	%
Monocytes/Macrophages, Body Fluid	21	%
RBC Count	5000 (H)	<1000/cmm
WBC Count	3612 (H)	0 - 5/cmm
Albumin, Fluid	1.8	g/dL
Amylase, Fluid	46.1	U/L
Glucose, Fluid	139	mg/dL
LDH, Fluid	179	U/L
Protein, Fluid	5.8	g/dL
Cholesterol, Pleural Fluid	34	mg/dL
Neutrophils, Body Fluid	42	%

tient was started on fluconazole 800 mg daily. Over the subsequent six months of antifungal treatment, his CF levels had decreased from 1:1024 to 1:64, reflecting a 16-fold reduction in titers. Repeat chest imaging showed interval improvement in the right pleural effusion, though stable reticulonodular interstitial opacities in lung parenchyma and lymphadenopathy. Given the observed clinical and radiographic improvements, along with significant decreases in serological markers, there was substantial evidence of a positive response to the antifungal treatment.

3. Discussion

Though recent cases of disseminated coccidiomycosis mimicking malignancy (and vice versa) have been described [3,6–8], our case highlights disseminated coccidioidomycosis manifested with rare and extensive micro nodularity of endotracheal and endobronchial lesions in an immunocompetent patient without eosinophilia on pleural fluid analysis. Additionally, airway involvement in coccidioidomycosis is a rare complication acquired by direct airway infection but might also be present from extrinsic compression from lymphadenopathy, most commonly in children [9]. Polesky et al. described a case series of 28 patients, six of which had tracheal involvement alone, as seen in the presented patient [9]. Bronchoscopic descriptions may vary widely and include mass lesions, nodules, granules, papillary excrescences, and patches, representing a spectrum from mucosal or submucosal infection and inflammation to intraluminal mass lesions [9–11]. Patients with a history of smoking, chronic cough, and weight loss, require evaluation for lung malignancy. However, physicians in endemic areas must also consider disseminated coccidioidomycosis, as nontuberculous mycobacteria may also present similar vague symptoms in combination with a solitary nodule, mass, or mass-like consolidation. This necessitates prompt serologic and bronchoscopy evaluations for early detection and the initiation of appropriate management [13].

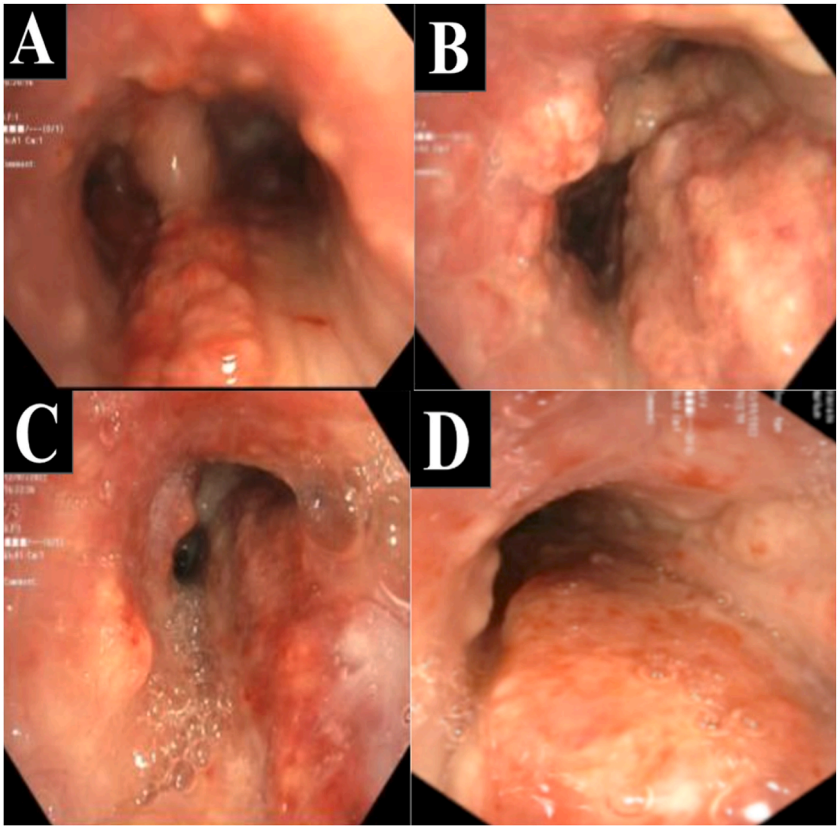

Fig. 3. Bronchoscopy images of airway lesions. (A) Multiple nodules in the lower trachea. (B) Near obstruction in the Right Main Stem Bronchus (RMSB). (C) Near obstruction in Right Upper Lobe (RUL) Bronchus. (D) Large nodule in the lateral wall of Left Main Stem Bronchus (LMSB).

There is limited data regarding the exact prevalence of lung infections mimicking cancer in the U.S. The spectrum of these infections differs geographically, which can affect the timeliness of diagnosis. Rolston et al. reported that 1.3% of patients referred for lung cancer evaluation at a center in Texas were actually diagnosed with an infection, with fungal infections accounting for 46% of these cases [12]. This underlines the importance of medical practitioners maintaining a high degree of vigilance for infectious etiologies in their differential diagnoses, particularly in endemic areas. A thorough understanding of lung cancer mimickers in these specific geographic contexts is essential to ensure timely investigation and initiation of appropriate treatment, thereby preventing the progression to advanced and potentially life-threatening disease.

Several factors increase the risk of disseminated coccidioidomycosis: HIV/AIDS, use of immunosuppressive medications, advanced age, diabetes, late-stage pregnancy, and certain racial/ethnic backgrounds (African American, Filipino, and Hispanic populations) [5,14,15]. Additionally, occupational, recreational, and environmental exposures contribute to infections as they directly introduce Coccidioides spores to the respiratory system [14]. This patient, while not immunocompromised, demonstrated advanced age, diabetes, recreational exposure in an endemic area (gardening in Arizona), and African American ethnicity as significant risk factors. When coccidiomycosis is suspected, serological testing remains a cornerstone in establishing the diagnosis.

The Infectious Disease Society of America (IDSA) and American College of Chest Physicians (CHEST) indicate that Coccidioides IgM antibody can be detected 7–21 days following the onset of symptoms, where higher titers potentially indicate extrapulmonary dissemination [4,14,16,17]. Initial Coccidioides Antibody with complement fixation (CF) in this patient was significantly positive with a high titer of 1:1024, where skin biopsy and histopathology confirmed disseminated coccidiomycosis. Coccidioides IgG antibodies detected through Coccidioides CF become detectable 21–35 after symptom onset, with peak titers often observed between days 21–70 [2,16]. However, in disseminated disease, CF antibody titers $>1{:}16$ have poor positive predictive value and may cross-react with other fungal species [14,17]. Therefore, serological testing must be supported by other elements of investigation to reinforce the diagnosis of disseminated coccidioidomycosis. In our case, radiographic imaging was complemented by serological testing, bronchoscopy, pleural fluid analysis, and positive tracheal biopsy. During the early stages of disease, antibody titers may be low or even negative before seroconversion so repeat testing after two weeks is recommended to improve detection [1,2,16,18]. Serial testing of antibody titers allows for identifying recurrence or response to treatment [2,16,17]. However, patients who are immunocompromised or taking immunosuppressants pose a challenge, as antibody titers may be highly variable. Urine antigen testing may be a viable alternative in this subset of patients [14].

In addition to clinical and radiographic findings, this patient presented with atypical pleural fluid analysis that deviates from the common characteristics of Coccidioides pleural effusions. Pleural effusions occur in 10–15% of patients with coccidioidomycosis,

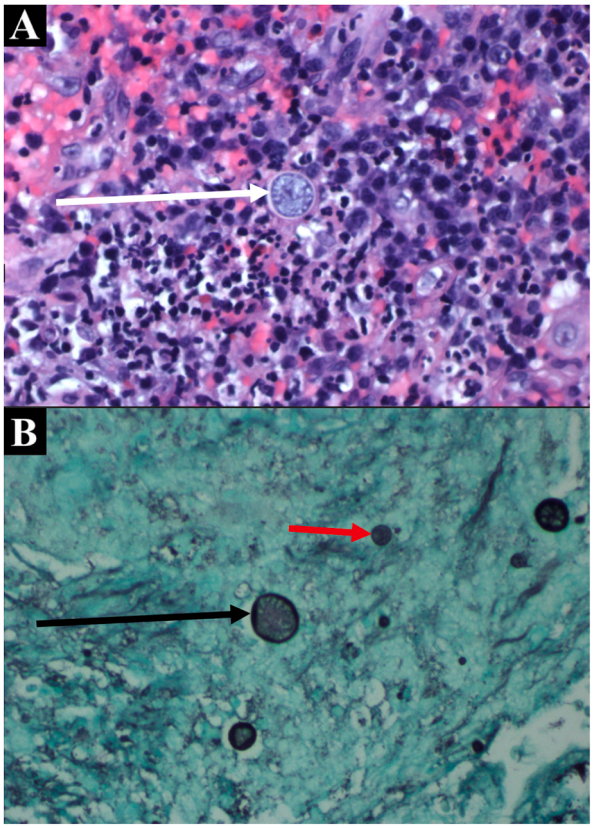

Fig. 4. Microscopic examination of endotracheal biopsy specimens with special fungal stains for enhanced visualization of fungal structures. (A) Periodic Acid-Schiff (PAS) stain effectively highlights the fungal cell walls, with the spherules of Coccidioides (White arrow) at a magnification of 400 × . (B) Gomori Methenamine-Silver (GMS) stain showcases intact spherules of Coccidioides, which are darkly stained with thick walls (Black arrow), and scattered released endospores (Red arrow) from ruptured spherules.

with 22.7% progressing to empyema. Studies predominantly indicate a lymphocytic exudate (average 58 + 7.55%) with monocytic (5.5 + 1.36%) and eosinophilic predominance (10.3 + 4.65%) [2,18,19]. In this case, the pleural effusion was classified as an exudate based on protein criteria, without meeting Light's lactate dehydrogenase ratio of 0.6, and exhibited a low pleural fluid cholesterol level. Furthermore, while Merchant et al. characterized these pleural effusions as eosinophilic, our patient presented with an exudative effusion lacking eosinophils. It is important to note that the sample size of the studied cohort was small (n = 12), and the authors suggested that more studies are needed to thoroughly characterize the eosinophilic pleural effusions of coccidioidomycosis [19]. Such nuanced manifestations emphasize the need for astute clinical awareness, particularly in endemic regions, where early diagnosis and intervention can significantly influence patient outcomes.

Lastly, expanding literature has reported increasing frequency of coccidioidomycosis and COVID-19 co-infections. This patient did note a prior COVID-19 infection, however it did not require hospitalization six months prior. Though the correlation between these two infections is unclear, it is mainly thought to be due to Coccidioides reactivation from immune dysregulation during COVID-19 infection or predisposition to severe COVID-19 from prior or chronic pulmonary coccidioidomycosis [14].

4. Conclusion

Disseminated coccidioidomycosis is rare, particularly in immunocompetent individuals, and even rare to cause airway manifestations of nodular and mass-like lesions and can masquerade as metastatic lung cancer. A detailed social history, including travel to endemic areas and hobbies such as gardening and a meticulous physical exam, could prompt clinicians with a high index of suspicion for early recognition and appropriate management, leading to a more favorable outcome.

CRediT authorship contribution statement

Amir R. Reihani: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Naveen Jayakumar:** Writing – review & editing, Validation, Supervision. **Ricardo Searcy:** Writing – review & editing, Writing – original draft, Data curation. **Anderson N. Vu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Formal analysis, Data curation, Conceptualization. **Anil Perumbeti:** Writing – review & editing, Validation, Supervision, Project administration,

Methodology, Funding acquisition, Data curation, Conceptualization. **Justin Thomas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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