Candida pneumonia with severe clinical course, recovery with antifungal therapy and unusual pathologic findings

A case report

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Abstract

Background: *Candida* is frequently isolated from the respiratory tract and usually reflects airway colonization. True *Candida* pneumonia is rare. Our aim is to document a case of *Candida* pneumonia confirmed by cultures, molecular techniques, and surgical lung biopsy, and to highlight a previously unreported pathologic manifestation of this infection.

Case summary: A 59-year-old man with a history of chronic obstructive pulmonary disease (COPD) presented with dry cough, low-grade fever, and progressive dyspnea. He was eventually diagnosed with sarcoidosis based on bilateral lung infiltrates and granulomas in a transbronchial biopsy. His condition worsened after immunosuppression, prompting surgical lung biopsy, which revealed suppurative granulomas containing *Candida albicans*, confirmed by cultures and polymerase chain reaction. Despite multiple episodes of respiratory failure and a prolonged course in intensive care, he recovered fully after antifungal therapy and is currently alive with COPD-related dyspnea 3 years after his initial presentation.

Conclusion: *Candida* can rarely cause clinically significant pneumonia in adults, and should be considered in the differential diagnosis of suppurative granulomas in the lung.

Abbreviations: BAL = bronchoalveolar lavage, COPD = chronic obstructive pulmonary disease, CT = computed tomogram, GMS = Grocott methenamine silver, IDSA = infectious diseases society of America, NCEZID = national center for emerging and zoonotic infectious diseases, PCR = polymerase chain reaction.

Keywords: *Candida albicans*, granulomas, lung, pathology, pneumonia

1. Introduction

According to a recent infectious diseases society of America clinical practice guideline, *Candida* is frequently isolated from the respiratory tract of patients who are in the intensive care unit and are intubated or have a chronic tracheostomy.[1] The guideline further states, 'this almost always reflects colonization of the airways and not infection. *Candida* pneumonia and lung abscess are very uncommon'. Given the rarity of bona fide cases of *Candida* pneumonia and the difficulties in diagnosis caused by

colonization, definitive diagnosis requires histologic evidence of fungal infiltration within lung tissue, which is considered the gold standard.[1–3]

Candida pneumonia has been reported in severely immuno-compromised individuals with disseminated disease, extremely low birth weight infants, and in patients with malignant tumors.[2–6] Disease isolated to the lungs in the absence of dissemination has been reported, but is less common. This form of the disease has been attributed to aspiration of organisms into the lungs from the upper airway.[7,8] Because issues with contamination complicate antemortem diagnosis, a definitive diagnosis of invasive *Candida* pneumonia requires histologic confirmation, which is generally obtained only at autopsy.[2,3,5–8] Reports in which an antemortem diagnosis of *Candida* pneumonia was made were usually based on positive cultures of sputum and/or bronchoalveolar lavage (BAL) fluid without histologic confirmation. Well-illustrated cases of microbiologically confirmed and histologically proven *Candida* pneumonia are rare. We are aware of only 1 case (of *Candida dubliniensis* pneumonia) in which the diagnosis was confirmed by microbiologic cultures, biopsy, and polymerase chain reaction (PCR).[9] The aim of this report is to document a case of *Candida* pneumonia confirmed by 3 modalities (cultures, PCR, histology) and manifesting with a hitherto unreported pathologic reaction. As per our Institution review board's policy, ethical approval is waived for case reports. Informed consent was not obtained as there is no patient-identifying information in this manuscript.
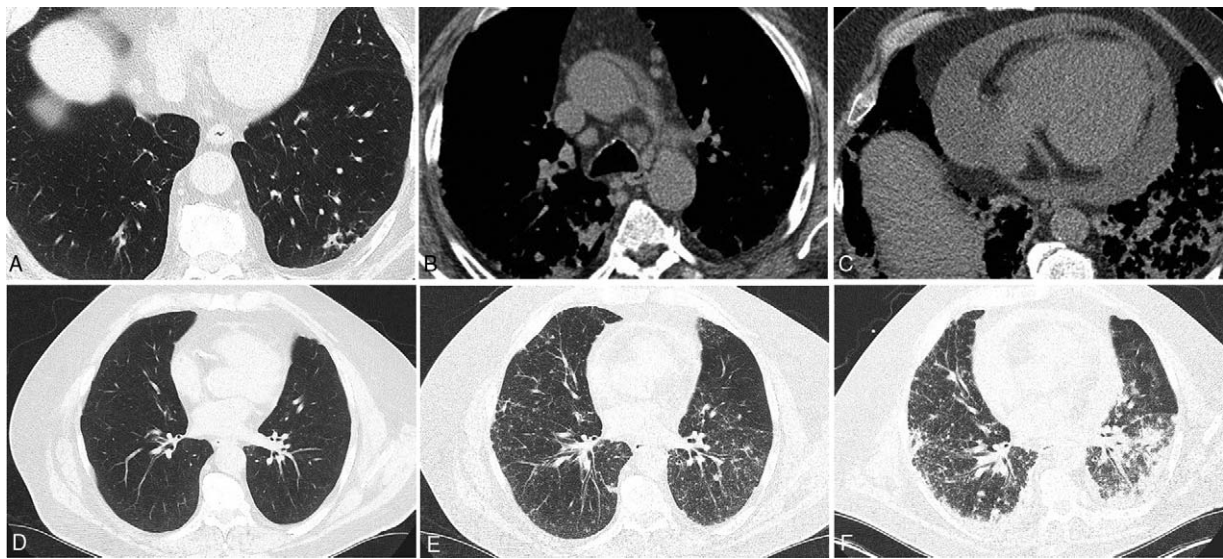
Figure 1. Chest CT findings. (A) Cluster of tiny lung nodules in the lower lobe of the left lung associated with mild peribronchial consolidation (1 month prior to presentation). (B) Mild mediastinal lymphadenopathy. (C) Circumferential pericardial effusion (day 20). (D–F) Progression of disease characterized by increase in size and number of lung nodules (D: 1 month prior to presentation, E: day 8, F: day 20). In part F, many nodules are subpleural and/or distributed along peribronchovascular interstitium, with new/worse patchy peribronchial consolidation, mainly in the lower lobes. Small pleural effusions are also present. CT = computed tomogram.

2. Case presentation

A 59-year-old man with a history of chronic obstructive pulmonary disease (COPD), type 2 diabetes, and ulcerative colitis (on intermittent prednisone) presented with dry cough, low-grade fever, and progressive dyspnea. He was a cigarette smoker (1–1.5 packs/d for 40 years, quit 10 weeks ago). Five months previously, he had presented with an episode of tussive syncope. On subsequent workup, peripheral opacities were noted on a computed tomogram (CT) of the chest. At the current time, chest CT showed a cluster of tiny lung nodules in the left lower lobe associated with mild peribronchial consolidation (Fig. 1A) and mild mediastinal lymphadenopathy (Fig. 1B). A ventilation perfusion scan performed to rule out pulmonary embolism showed no mismatched defects. He was diagnosed with pneumonia, treated with levofloxacin and corticosteroids, and discharged on oral antibiotics and oral methylprednisolone. A week later, he was readmitted with persistent cough, fever, and dyspnea. Chest CT showed interval progression of lung opacities, which were now bilateral and interstitial. He received vancomycin and meropenem for 3 days, but after increasing shortness of breath and rales on examination, he was started on intravenous methylprednisolone. Given the combination of mediastinal lymphadenopathy and worsening bilateral interstitial infiltrates despite antibiotic therapy, noninfectious possibilities were considered. On day 9, he underwent transbronchial lung biopsy and BAL. Cultures of the BAL fluid from his second admission were preliminarily reported as growing *Candida*. The biopsy revealed nonnecrotizing granulomas (Fig. 2). No organisms were found on acid-fast or Grocott methenamine silver (GMS) stains. He was diagnosed with sarcoidosis and discharged on oral prednisone.

Four days later (day 20 from his initial presentation), he presented with worsening dyspnea, weakness, night sweats and fever, and was readmitted. His prednisone had previously been increased to 60 mg daily but his symptoms had failed to improve and he had become increasingly hypoxic (oxygen saturation 77%

on 4 liters oxygen by nasal cannula). He developed respiratory acidosis with worsening renal function. Chest CT showed new-onset pericardial effusion (Fig. 1C), progressively confluent airspace opacities in the lower lobes, progression of the nodular component in the mid to upper lung fields, and mediastinal lymphadenopathy. The progression of radiologic findings between the initial CT 1 month prior to presentation and the CT on day 20 is shown in Fig. 1 D to F. Echocardiography showed new-onset moderate pericardial effusion requiring pericardial window creation that drained 400 mL of fluid. Thoracoscopic wedge biopsies of the lung (right middle and lower lobes) were performed on day 22, and a pericardial window was created, which yielded 400 mL of pericardial fluid.
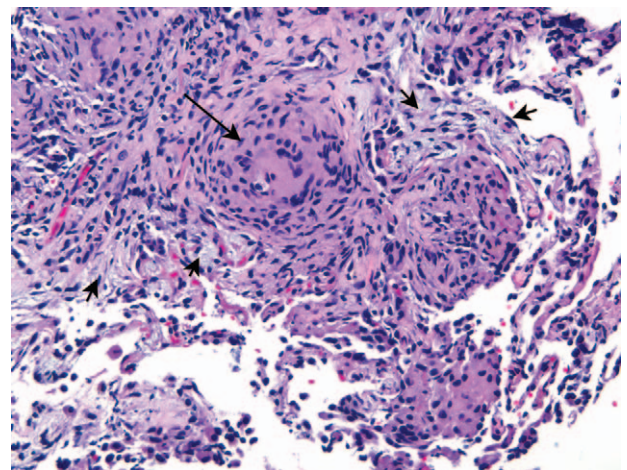

Figure 2. Transbronchial lung biopsy (day 9). Nonnecrotizing granuloma (long arrow) is present in a background of organizing pneumonia (short arrows). The latter finding is a clue that the etiology is not sarcoidosis, but was originally overlooked (hematoxylin and eosin, X200).
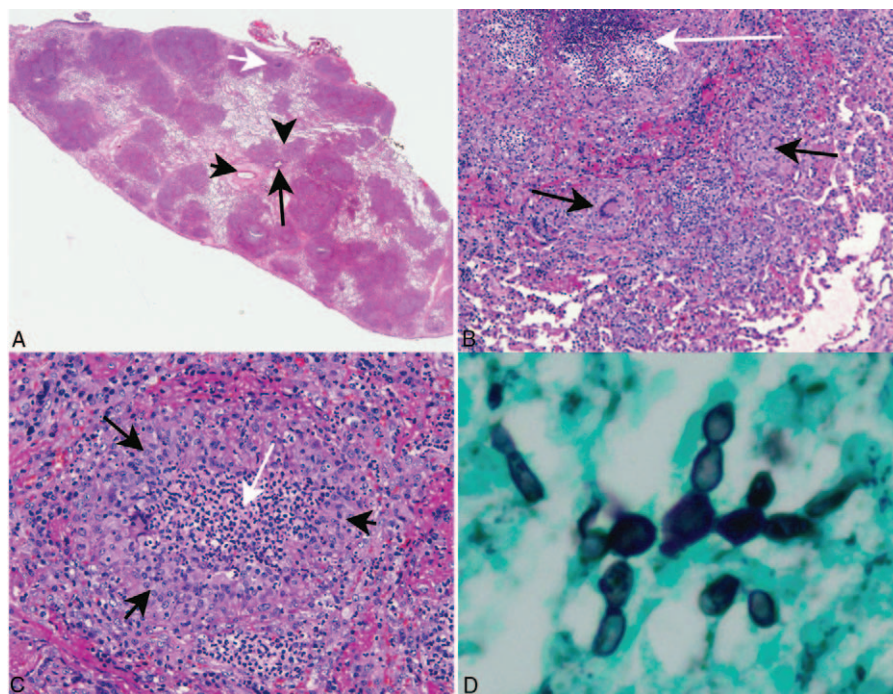
Figure 3. Surgical lung biopsy. (A) Scanning magnification showing a nodular, bronchopneumonia-like histologic picture (hematoxylin and eosin, X0.5). Short arrow: small pulmonary artery branch, long arrow: bronchiole, arrowhead: inflammatory infiltrate causing consolidation in peribronchiolar lung. The area indicated by the white arrow is shown at higher magnification in B. (B) High magnification shows occasional nonnecrotizing granulomas (black arrows) similar to those seen in the prior transbronchial biopsy adjacent to larger suppurative granuloma (white arrow). (C) Suppurative granuloma at high magnification. Black arrows: granulomatous rim, white arrow: suppurative necrosis (hematoxylin and eosin, X200). (D) Fungal pseudohyphae and a few yeasts were seen in the suppurative areas on Grocott methenamine silver stain (original magnification X1200).

He was given 125 mg of intravenous methylprednisolone and broad-spectrum antibiotics including amphotericin B.

The surgical lung biopsies showed extensive suppurative granulomatous inflammation involving >50% of the lung parenchyma (Fig. 3A–C). The process was prominent adjacent to bronchioles, mimicking acute bronchopneumonia (Fig. 3A). The suppurative granulomas contained a neutrophil-rich (abscess-like) necrotic center and a granulomatous periphery composed of epithelioid histiocytes and occasional multinucleated giant cells (Fig. 3C). Within the necrotic centers, fungal organisms (mainly pseudohyphae, and a few yeasts) were identified on GMS stains (Fig. 3D). Pericardial tissue also showed extensive suppurative granulomatous inflammation histologically identical to the lung. Subsequently, cultures of sputum, BAL fluid, pericardial fluid, and the lung biopsies all grew *Candida albicans*. The organisms were susceptible to micafungin and fluconazole. Multiple blood cultures were negative.

For further workup, formalin-fixed paraffin-embedded tissue from the surgical lung biopsies of the right middle and lower lung lobes as well as the pericardium was sent to the national center for emerging and zoonotic infectious diseases (NCEZID). Immunohistochemical staining performed at the NCEZID using a rabbit polyclonal antibody against *Candida albicans* was strongly positive for this fungal organism. PCR analysis using the pan-fungal primer set ITS3/ITS4 amplified *Candida albicans* from the paraffin-embedded tissues of the right middle and lower lung lobes, providing further confirmation of the diagnosis.

The entire timeline of events is shown in Table 1. The patient underwent a severe and protracted (70 days) clinical course including episodes of respiratory failure, an episode of cardiac arrest, multiple intubations, and eventual tracheostomy. He was switched from intravenous liposomal amphotericin B (days 20–53) to intravenous micafungin (days 54–59) and eventually to a 9-month course of oral fluconazole (days 60–281), with complete resolution of infection-related symptoms. A follow-up chest CT performed 1 year later showed resolution of nodules and infiltrates (Fig. 4). He is currently alive (age 63) with multiple medical issues including COPD-related dyspnea 3 years after his initial presentation.

3. Discussion

To our knowledge, this is the first reported case of *Candida albicans* pneumonia confirmed by a combination of surgical lung biopsy, microbiologic cultures and molecular identification, and causing suppurative granulomas in the lung. This case provides several valuable lessons for clinicians as well as pathologists. First, the diagnosis of sarcoidosis must be made with caution in immunocompromised, febrile patients. In this setting, a diagnosis of sarcoidosis must not be considered definitive unless mycobacterial and fungal cultures have been reported as negative. Second, nonnecrotizing granulomas can occur in mycobacterial and fungal infections. They are usually admixed with necrotizing granulomas, but the latter can easily be missed in small biopsies. Clinicians should not consider a pathologic diagnosis of 'nonnecrotizing granulomas' to mean that the diagnosis of sarcoidosis has been 'confirmed'. In lung biopsies with non-necrotizing granulomas, pathologists should look for histologic clues that argue against the diagnosis of sarcoidosis, such as organizing pneumonia.[10,11] Third, albeit rare, invasive *Candida* pneumonia is a bona fide, clinically significant entity.

Table 1

Timeline.

Day	Event
Day 1	Admitted for cough, shortness of breath, fever. Treated with levofloxacin and corticosteroids
Day 2	Discharged
Day 8	Readmitted for worsening cough, shortness of breath, fever and night sweats. Chest CT (Fig. 1 E): interval progression of lung opacities. Vancomycin and meropenem started
Day 9	Transbronchial biopsy performed
Day 11	Increasing shortness of breath. BAL: neutrophilic predominance, KOH negative. No improvement on antibiotics. Sarcoidosis considered in differential diagnosis. Intravenous methylprednisolone 40 mg every 8 h started
Day 12	p-ANCA immunofluorescence positive, myeloperoxidase antibody positive: 4.1, c-ANCA immunofluorescence negative, proteinase 3 negative
Day 13	Transbronchial biopsy reported as 'nonnecrotizing granulomatous inflammation'
Day 14	Clinical diagnosis: most likely sarcoidosis; intravenous corticosteroids continued, antibiotics discontinued. Patient feeling better
Day 15	Discharged on prednisone 30 mg/d
Day 19	Severe shortness of breath and hypoxia (O2 sat 77% on 4L nasal cannula). BAL preliminary report: *Candida albicans*
Day 20	Admitted to intensive care unit. Chest CT: progression of infiltrates and development of pericardial effusion (Fig. 1C,F). Infection suspected, corticosteroids discontinued. Intravenous liposomal amphotericin B started
Day 22	Surgical lung biopsy and pericardial biopsies performed. Budding yeasts identified in microbiology specimen from lung biopsy
Day 24	Worsening fever, and development of acute kidney injury moved to larger hospital with advanced intensive care unit
Day 25	Cultures from surgical lung biopsy and pericardial fluid: *Candida albicans* (reported 5 days after biopsy)
Day 27	Creatinine clearance 58 mL/min
Day 32	Extubated
Day 33	*Candida albicans* confirmed by PCR of surgical lung biopsy performed at outside reference laboratory
Day 42	Possible aspiration event, followed by ventricular tachycardia and cardiac arrest. Intubated and resuscitated
Day 46	Chest CT shown in Fig. 4A
Day 47	Extubated
Day 48	Reintubated
Day 49	Tracheostomy
Day 54	Amphotericin B stopped, micafungin started (150 mg IV daily)
Day 60	Switched to fluconazole (400 mg PO daily)
Day 70	Discharged
Day 159	Cough and emesis: continuing suppressive fluconazole therapy
Day 249	Aspiration pneumonia; still on fluconazole
Day 281	Fluconazole stopped
Day 330	Chest CT shown in Fig. 4B

ANCA = antineutrophilic cytoplasmic antibody; BAL = bronchoalveolar lavage; CT = computed tomogram; IV = intravenous; KOH = potassium hydroxide; MPO = myeloperoxidase; PCR = polymerase chain reaction; PO = per oral.

Appropriate antifungal therapy treatment can be effective, as shown by amelioration of symptoms and resolution of radiologic infiltrates in this case. Clinicians should not dismiss positive cultures for *Candida*, especially if the cultured specimen is normally sterile (BAL, biopsied lung tissue, pericardial fluid).

This report also provides valuable pathologic information regarding the inflammatory reaction in the lung in response to *Candida*. Most reports that mention the pathologic findings in *Candida* pneumonia report 'bronchopneumonia' or 'abscesses' as the main findings.[2,5,7,8,12,13] To our knowledge, no prior report has documented suppurative granulomas as a tissue response to *Candida albicans* infection in the lung. Suppurative granulomas are a type of necrotizing granuloma in which the necrotic center of the granuloma is composed of suppurative
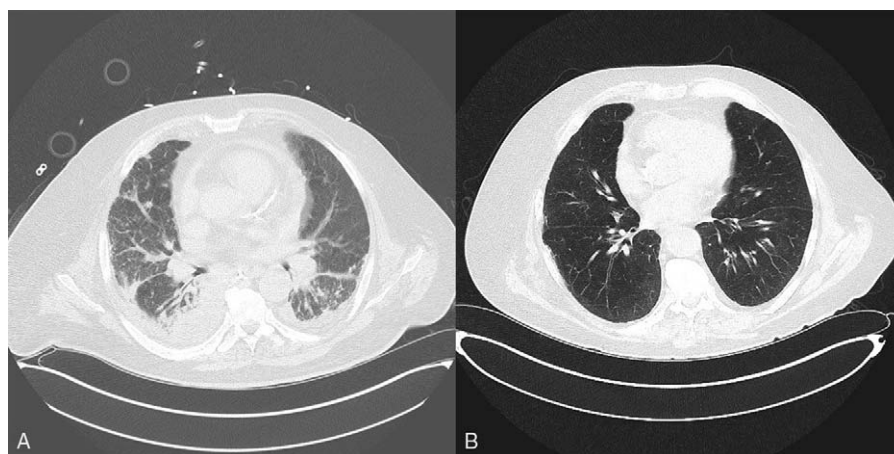

Figure 4. Chest CT. (A) One month after surgical biopsy (day 46). (B) Day 330. CT = computed tomogram.

necrosis rich in neutrophils. Such lesions can be misinterpreted as acute inflammation, bronchopneumonia, or abscess if the granulomatous rim is not appreciated. In the lung, suppurative granulomas are most characteristic of blastomycosis, but they also occur in aspiration of food/particulate matter, and granulomatosis with polyangiitis.[10,11] In lymph nodes, the differential diagnosis of suppurative granulomas includes cat scratch disease, tularemia, yersiniosis, lymphogranuloma venereum, brucellosis, and nontuberculous mycobacterial infection.

4. Conclusion

We describe the clinical course and pathologic findings in a case of *Candida* pneumonia in which the diagnosis was confirmed by histopathology, microbiologic cultures, and molecular methods. Although the infection was severe and life threatening and the clinical course was protracted, the patient eventually recovered fully with appropriate antifungal therapy. *Candida albicans* can rarely cause clinically significant pneumonia in adults, and should be added to the list of causes of suppurative granulomas in the lung.

Acknowledgement

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