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Case Report

# Acute respiratory distress syndrome due to *Cryptococcus albidus* pneumonia: Case report and review of the literature

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Although cryptococcal infections due to *Cryptococcus neoformans* are frequently reported in the immunosuppressed patients, infections related to other *Cryptococcus* spp. are rarely reported. We are reporting a case of pulmonary infection and ARDS due to *C. albidus* in a patient receiving immunosuppressive therapy because of Still's disease. The diagnosis was made by tissue biopsy and culture. The patient responded to treatment with amphotericin B lipid complex 400 mg/day. The case is significant in that it reminds of yeasts as a cause of community acquired infection in the immunosuppressed patients.

**Keywords** *Cryptococcus albidus*, pneumonia, acute respiratory distress syndrome

## Introduction

Cryptococcosis is a serious infection, primarily caused by *Cryptococcus neoformans* and is of special importance in immunosuppressed patients [1]. *Cryptococcus* spp. are worldwide in distribution and are frequently isolated from soil contaminated with bird feces, especially of pigeons [2]. *C. neoformans* is noted for a particular predilection for the meninges especially in immunosuppressed patients [1]. *Cryptococcus albidus*, a non-*C. neoformans Cryptococcus* spp., is an encapsulated yeast, that is rarely isolated as a human pathogen. But when involved in infections, it is generally considered to have been acquired via the respiratory system. To the best of our knowledge there have been only three reports of pulmonary involvement due to *C. albidus* [3–5]. In the first two there was only pulmonary involvement [3,4], while in the third the yeast caused a disseminated infection in a patient with renal failure [5]. We report another case of *C. albidus* pneumonia complicated by acute respiratory distress syndrome (ARDS), in a patient with Still's disease.

## Case report

A 44-year-old man, who was under immunosuppressive therapy because of Still's disease, was admitted to our intensive care unit in acute respiratory failure. His history consisted of fever, dry cough and dyspnea of two weeks duration. He did not have any pulmonary problems prior to this episode. His past medical history was unrevealing except for Still's disease for which he was being treated with low dose steroids and methotrexate for the previous 6 months. He smoked 25 packs of cigarettes per year, did not consume alcohol, nor used any drugs. Blood pressure, pulse, respiratory rate and body temperature were 107/65 mmHg, 85/min (regular), 32/min and 36.7°C, respectively. Auscultation revealed basilar rales over the right lung. Cardiac

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evaluation was normal. He did not have organomegaly, lymphadenopathy or any nodular lesions. Neurological examination was within normal limits. He was started on clarithromycin with the suspicion of atypical pneumonia. However, because of increasing dyspnea that restricted his daily activities and ongoing fever, he was hospitalized. His chest radiography showed bilateral basilar interstitial reticulonodular lesions. Degree of hypoxemia increased progressively and the patient had to be intubated and mechanical ventilation was started, because of pneumonia associated acute respiratory distress syndrome (ARDS). After blood, tracheal aspirate, and urine specimens were obtained for culture to evaluate the presence of *Pneumocytis jirovecii*, fungi, viruses, treatment with levofloxacin and trimethoprim-sulfamethoxazole was initiated. Thoracic tomography revealed bilateral patchy infiltration and ground glass appearance consistent with the radiological findings of ARDS (Fig. 1). Septic shock and disseminated intravascular coagulation with severe thrombocytopenia developed. Microbiological and serological studies for *Legionella*, HIV, *Pneumocystis jirovecii*, CMV, and tuberculosis were all negative. Open lung biopsy was performed as a diagnostic procedure and microscopic examination of samples of the lung tissue revealed diffuse, interstitial inflammation and fibroblastic proliferation in the lung parenchyma. Hyperplasia of the alveolar epithelium was observed, and remnants of hyaline membranes were present (Fig. 2). Histopathological findings were compatible with diffuse alveolar damage. In addition, yeast-like structures were seen within the alveolar spaces in periodic acid-Shift stained material (Fig. 3). Gram stained smears prepared from the fresh tissue sample showed yeast cells (Fig. 4). Cultivation of the specimen yielded yeast colonies which were identified as *Cryptococcus albidus*, based on the ID32C (bioMerieux,

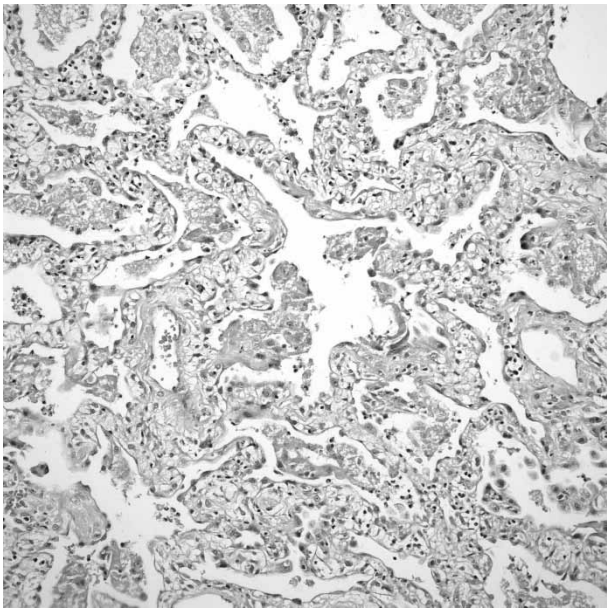

**Fig. 2** Histopathological examination of the lung tissue showing diffuse, interstitial fibroblastic proliferation, 722 × 722 mm (72 × 72 DPI).

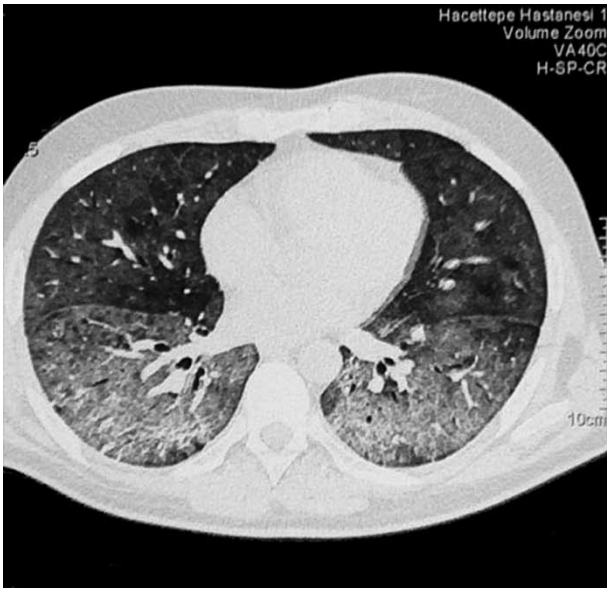


**Fig. 1** Thoracic tomography showing bilateral patchy infiltration and ground glass appearance consistent with the radiological findings of ARDS, 127 × 122 mm (100 × 100 DPI).

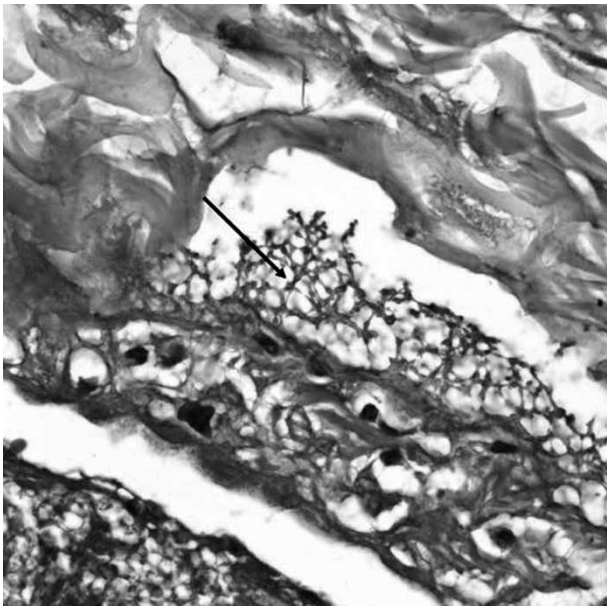

**Fig. 3** PAS positive yeast like structures (arrow) are seen within the alveolar spaces.

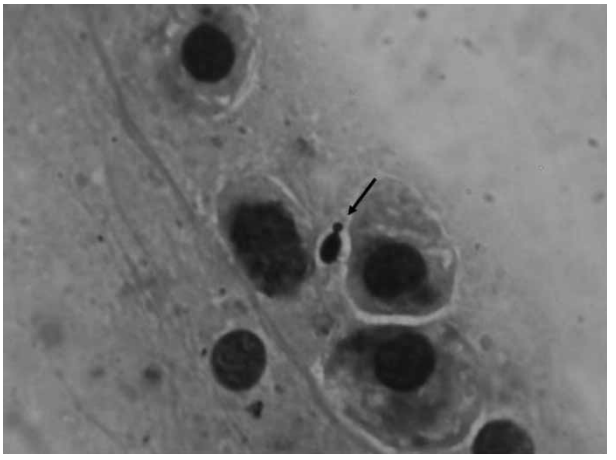

**Fig. 4** Gram stained smears prepared from the fresh tissue sample showed budding yeast cells (arrow).

France) assimilation profile, morphology on cornmeal Tween 80 agar, positive urease activity, favorable growth at 30°C and poor and slow growth at 37°C [6]. Nitrate assimilation test was positive. The isolate was sent to the Mycology Laboratory of the National Center for Microbiology of Spain for molecular identification. For this procedure the yeast was cultured in YEPD medium (0.3% yeast extract, 1% peptone, 2% dextrose), and grown overnight at 37°C. Yeast cells were recovered and subjected to a DNA extraction protocol [7]. DNA segments comprising the region ITS1 and ITS2 were amplified with primers ITS1 (5′ TCCGTAGGTGAACCTGCGG 3′) and ITS4 (5′ TCCTCCGCTTATTGATATGC 3′). Reaction mixtures contained 0.5 μM of each primer, 0.2 mM of each DNTP, 5 μl of PCR buffer 10 × (Applied Biosystem, Madrid, Spain), 2.5 U Taq DNA polimerase (Amplitaq, Applied Biosystem) and 5 ng of DNA in a final volume of 50 μl. The samples were amplified in a GeneAmp PCR System 2400 (Applied Biosystem). Sequence reactions were done using 4 μl a DNA sequencing kit (BigDye Terminator Cycle Sequencing Ready Reaction, Applied Biosystem), 1 μM of the primers (ITS1 and ITS4) and 5 μl of the PCR product in a final volume of 10 μl. Sequences were assembled and edited using the SeqMan II and EditsEq software packages (DNAstar, Inc. Lasergene, Madison, USA). The sequence analysis was performed by comparison with the nucleotide sequences of reference isolates obtained from the GenBank (http://www.ncbi.nih.gov/Genbank/) and from the database of the Department of Mycology of the Spanish National Center for Microbiology. Analysis was done with the help of Fingerprinting II informatix software, version 3.0 (BIORAD, Madrid, España). Phylogenetic analyses were also conducted using maximum parsimony clustering. Phylogram stability was assessed via parsimony bootstrapping with 1000 simulations. Phylograms were outgroup rooted with *C. neoformans* (CBS 132). After analyzing DNA segments comprising the region ITS1 and ITS2 and comparing them with the reference strains, the sequence of the clinical isolate matched the patterns of those of *C. albidus* isolates. Percentages of similarity were 99.2%.

Broth microdilution susceptibility testing was performed as described in the NCCLS document M27-A2 [8]. Minimal inhibitory concentrations were as follows: Amphotericin B 0.50 mg/l, flucytosine 64 mg/l, fluconazole 128 mg/l, itraconazole 16 mg/l, voriconazole 16 mg/l, posaconazole 16 mg/l, and caspofungin 32 mg/l.

Tissue cultures for tuberculosis, aerobic bacteria and CMV PCR were negative. Upon reinterrogation, the family indicated that the patient used to deal with birds, especially pigeons, as a hobby. Amphotericin B lipid complex at a dose of 400 mg/day was added to the antibiotic regimen. It is recommended that patients with *C. albidus* should have an examination of their cerebrospinal fluid (CSF) [9]. Yet CSF examination for *C. albidus* could not be performed because of severe thrombocytopenia. Follow-up chest X-rays showed gradual regression of the infiltrates after day 5 and the degree of hypoxemia resolved significantly. However, on day 3, during routine daily interruption of the sedatives, the patient was found to be unresponsive. Subsequent computed tomography of the brain revealed subarachnoid hemorrhage. The patient died on the 10th day of amphotericin B therapy.

## Discussion

Cryptococcal infections commonly start after inhalation of the pathogen and the lung is classically the primary site of infection [1], with *C. neoformans* as the primary etiologic agent. However, cases of pneumonia caused by other species have been occasionaly reported [1]. Although birds are thought to be reservoirs for *Crytptococcus* spp., this is somewhat controversial with respect to the non-*C. neoformans Cryptococcus* species. However Rosario *et al*. [2] recently reported the isolation of *C. uniguttulatus, C. laurentii, C. albidus* from cloaca of pigeons. Similarly, there have been other reports of isolation of *Cryptococcus* species, and of *C. albidus* from pigeons and other pet birds [10]. Although studies of the pigeons our patient was breeding were not possible, they were considered to be a possible source of his infection since there were no other risk factors.

Although *C. albidus* is such a rare cause of disease that it is generally considered to be non-pathogenic [11], this opportunistic yeast has previously been reported to have been isolated from cerebrospinal fluid [12–14], blood [9,15–19], lung [3] and pleural space [4] and skin [5,20]. Almost all cases developed in immunosuppressed patients, mostly in those with AIDS. There are also several reports of corneal transplant infections [21,22]. Systemic infections, fungemia have been described primarily in patients with defective cellular immunity.

In this case, a cryptococcal infection was not suspected clinically at the beginning, although a non-bacterial cause was being sought because of unresponsiveness of the patient to broad spectrum antibacterials. The diagnosis could only be made after the yeast was recovered in culture. Although a cryptococcal serum antigen assay was not available, the use of the test has been reported as undiagnostic in cases involved *C. albidus*. Despite sharing several capsular antigens with *C. neoformans*, negative results have been described in virtually all previous cases [4,15,16,20]. Therefore fungal culture or India ink preparation is recommended for demonstration of the organism [4,20].

Radiography may be unrevealing as well, because cryptococcal infections may not have specific radiological findings [1]. Nevertheless, three main patterns of involvement have been described, i.e., (i) solitary or multiple nodules, (ii) consolidation, often multifocal, patchy, segmental, or lobar; and (iii) interstitial micronodular or reticulonodular lesions. Cavitation, pleural effusions, hilar lymphadenopathy may also accompany these patterns. Differential diagnosis should include tuberculosis, histoplasmosis, aspergillosis, pneumocystosis, cytomegalovirus pneumonia, Kaposi's sarcoma and lung cancer. Zinck *et al*. [23], have reported computer tomography results of patients with proven pulmonary cryptococcosis, noting that 91% of the cases had pulmonary nodules, solitary or multiple, as the most common finding. Yet, it must be kept in mind that these results are from patients with *C. neoformans*, not *C. albidus*. Our patient had interstitial reticulonodular lesions on chest radiography and ground glass appearance and bilateral patchy type infiltration on computed tomography, which were considered to be non-specific and consistent with ARDS. Nodules that are more specific for fungal infections were not observed.

The antifungal activities against *C. albidus* are reported to be variable and there is no accepted treatment protocol for infections caused by this fungus. A recent study reported that amphotericin B and itraconazole were the only drugs active against *Cryptococcus albidus* [24].

Since there are very few reports of *C. albidus* infection, there is no consensus on treatment. There are only three earlier descriptions of the yeast's involvement in pulmonary infections [3–5]. In the first two, the infections were restricted to the lungs. The case described by Krumholz involved pneumonitis in a 68-year-old man with no known immunosuppression [3]. In contrast, Horowitz *et al*. presented a case in a 37-year-old black man with a history of end-stage renal disease who presented with a nodule on the chest wall and pleural effusion on chest radiography. *C. albidus* was isolated from the pleura, but the pulmonary parenchyma was not involved [4]. Both patients were treated with amphotericin B and survived. The third patient was a 23-year-old renal transplant recipient who was on immunosuppressive treatment. He had disseminated fungal infection and subsequent ARDS. Contrary to our patient, skin lesions developed and *C. albidus* was recovered in culture from skin specimens. He was successfully treated with fluconazole [5]. Our patient was treated with amphotericin B and showed marked clinical improvement, with the disappearance of hypoxemia and infiltrates on chest X-ray disappeared, but was lost because of intracranial hemorrhage.

This case is significant in that it is the second reported case of ARDS due to *C. albidus* pneumonia, and it was a diagnostic challenge as it could only be made by lung biopsy.

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