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Case Report

Cryptococcus albidus infected pulmonary mycosis with miliary nodules in CT imaging: Two case reports

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ABSTRACT

We presented two cases of Cryptococcus albidus fungemia in men who were identified with millary nodules by chest computed tomography (CT). They present cough and fever, with no other abnormal physical examination. The patients were treated successfully with a week-long course of voriconazole tablets. Accurate microbiological diagnosis of NGS and effective therapy as antifungal treatment of voriconazole tablet are critical for *C albidus* infection. Total of 18 cases of *C albidus* infection cases were identified from 2000 years to now, eight of which were invasive *C albidus* infection, and ten were noninvasive infection. None died cases were reported in noninvasive infection.

1. Introduction

Cryptococcus albidus, synonymous with Naganishia albida, is one of 70 types of Cryptococcus that causes opportunistic infection in immunocompromised patients. It can infect not only humans, but also dogs, cats, and marine mammals [1,2]. *C albidus* is one kind of ubiquitous saprophytic yeast that possesses a thick polysaccharide capsule that confers invasive and pathogenic capacity by enhancing its resistance to host defenses. Cryptococcus laurentii and *C albidus* account for 80 % of noninvasive Cryptococcus infections, being medically important systemic mycoses in immunocompromised adults over the past few decades [2] (see Table 1).

The CT imaging of Cryptococcus-infected pulmonary mycosis varied, with most of them shown as isolation nodules or lump types; multiple nodules or lump types; and rarely shown as infiltrating consolidation; and diffuse military shadow [3]. The military nodules are common to various diseases, with no single imaging feature being specifically diagnostic. The miliary pattern is thought to occur when organisms that have gained access to the bloodstream become lodged in the capillary beds and proliferate locally [4].

The clinical data and other associated imaging findings play an essential role in the differential diagnosis of millary micronodules. However, to our knowledge, no clinical case report has been reported on *C albidus* infected pulmonary mycosis with miliary nodules.

2. Case presentation

2.1. Case 1

One 66-year-old man was hospitalized with a 3-day cough, asthenia, and fever on November 04, 2023. He denied a medical history of hypertension, coronary artery disease (CAD), and diabetes mellitus. Computed tomography (CT) angiography revealed diffuse specks obscure shadows and millary nodules in both lungs, multiple lymph nodes in mediastinum and partial intumescence, and both

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Table 1
Literature review of reported *C albidus* infection cases.

References	Years	Places	Age (Years)	Sex	Underlying diseases	Lesion	Site of isolation	Treatment	Outcome
Invasive *C albidus* infection									
[14]	2001	Korea	23	M	Kidney TPL (Cyclosporine, steroid)	Disseminated cryptococcosis	Skin, lung tissue	Fluconazole	Survived
[15]	2003	Pennsylvania	51	M	DM, T-lymphoma, AML, SCT (chemotherapy)	Fungemia	Blood	AmpB, itraconazole	Survived
[16]	2006	Turkey	44	M	Still disease (immunosuppressive therapy)	Pneumonia complicated by ARDS	Lung tissue	AmpB	Died
[17]	2011	Greece	17 days	M	Premature, 27-week gestation	Fungemia	Blood	AmpB, 5-FC	Survived
[6]	2012	New York	57	M	HCV-associated cirrhosis, hypertension, T2DM, ESRD	Peritonitis	Peritoneal lavage fluid	Fluconazole, caspofungin, AmpB (7 days)	Survived
[20]	2013	Tennessee	55	M	Liver cirrhosis, liver TPL	Fungemia	Blood	Posaconazole (23 days)	Survived
[18]	2013	China	28	M	AIDS	Meningoencephalitis	CSF	Fluconazole, caspofungin, AmpB (7 days)	Died
[19]	2015	Hungary	83	M	Hypertension, chronic skin rash (steroid)	Pulmonary cryptococcus infection, primary cutaneous cryptococcosis	Sputum/skin	Fluconazole	Survived
Noninvasive *C albidus* infection									
[7]	2000	United Kingdom	70	M	DM, HTN, Sézary syndrome (methotrexate)	Cutaneous infection	Penile lesion	Fluconazole	Improved
[8]	2001	New York	16	M	AIDS	Scleral ulcer	Eye	AmpB, fluconazole	Improved
[9]	2005	South Carolina	69	F	Penetrating keratoplasty for Fuchs corneal dystrophy	Keratitis (donor transmitted)	Original donor cornea	Removal of transplanted cornea	Improved
[10]	2007	Kentucky	14	M	Refractory psoriasis (etanercept)	Localized cutaneous infection	Skin	Fluconazole	Improved
[11]	2011	Utah	83	M	Palmar pustular psoriasis (methotrexate, etanercept, adalimumab, efalizumab, tacrolimus ointment)	Generalized hemorrhagic plaques	Skin	Fluconazole	Improved
[12]	2015	Taiwan	45	M	None	Keratitis	Eye	AmpB, fluconazole	Improved
[13]	2017	Iran	29	M	None	Pityriasis versicolor	Skin	Itraconazole	Improved
[5]	2019	Greece	15	F	Takayasu arteritis and chronic recurrent multifocal osteomyelitis	Fungemia	Skin	5-FC, AmpB, fluconazole	Improved
This case	2023	China	69	M	None	Fungemia	Lung	Voriconazole	Improved
This case	2023	China	48	M	Hypertension	Fungemia	Lung	Voriconazole	Improved

pleura thickened slightly (Fig. 1A). At the time of hospitalization, some examinations were added. We found no abnormalities on prostate-specific antigen (PSA), cancer-related biomarkers (alpha-fetoprotein, carcinoembryonic antigen, CA199, CA125, CA153, CA50, CA242), proteinase 3 (PR3), *anti*-myeloperoxidase (MPO) antibody, blood transfusion associated (type B hepatitis B, hepatitis C, AIDS, and syphilis), fecal routinely, and fecal occult blood test (FOBT) detection. The erythrocyte sedimentation rate (ESR) is 47mm/h. M. Pneumonia (MP) antibody is 246 AU/mL. C-reactive protein (CRP) of 89.3mg/L. High sensitivity CRP (HS-CRP) of 88.4mg/L. Procalcitonin (PCT) of 4.47ng/mL. The blood gas indicators were measured, with pH of 7.439, partial pressure of carbon dioxide (PCO_2) of 36.9 mmHg, partial pressure of oxygen (PO_2) of 71.3 mmHg, oxygen absorbent of 3L/mm, and oxygenation index of 213 (type I respiratory failure). The complete blood count (CBC) detection showed that lymphocyte absolute value of 1.0×10^9/L, LY% lymphocyte of 12.2 %, eosinophil absolute value of 0.00×10^9/L, EOS% eosinophil of 0.0 %, granulocyte absolute value of 6.6×10^9/L, and GR% granulocyte of 81.2 %. Hemoglobin A1C (HbA1C) of 6.7 %. The biochemical indicator of albumin (ALB) of 32.3g/L, albumin/globulin ratio of 1.1, high-density lipoprotein cholesterol (HDL-C) of 0.47mmol/L, aspartate aminotransferase of 12.4U/L, the ratio of aspartate transaminase/alanine aminotransferase (AST/ALT) was 0.6, alkaline phosphatase (ALP) of 44U/L, urea of 10.11mmol/L, glucose of 10.87mmol/L, apolipoprotein A1 of 0.60g/L, lactate dehydrogenase (LDH) of 228U/L, inorganic phosphate of 0.81 mol/L, and total protein of 61.9 g/L. D-dimer of 3.68 mg/L. Fibrinogen of 6.951 g/L. After being admitted to the hospital, he accepted anti-infection treatment with Tazobactam Sodium/Piperacillin Sodium for 4 days. However, no signs of improvement were observed. Therefore, we added the examinations.

On 07/11, a flexible bronchoscope complicated with bronchoalveolar lavage (BAL) was performed to obtain tissues. Next-generation sequencing (NGS) results identified clustered Schizophyllum commune Fr., *Candida tropicalis*, and *C albidus*. The pathology on the lung showed chronic inflammation compilated with local coal dust deposits in the bronchial mucosa. After the NGS analysis, we replaced the anti-infection treatment with antifungal drugs of voriconazole tablet with 0.2g Bid for one week. The reexamina-

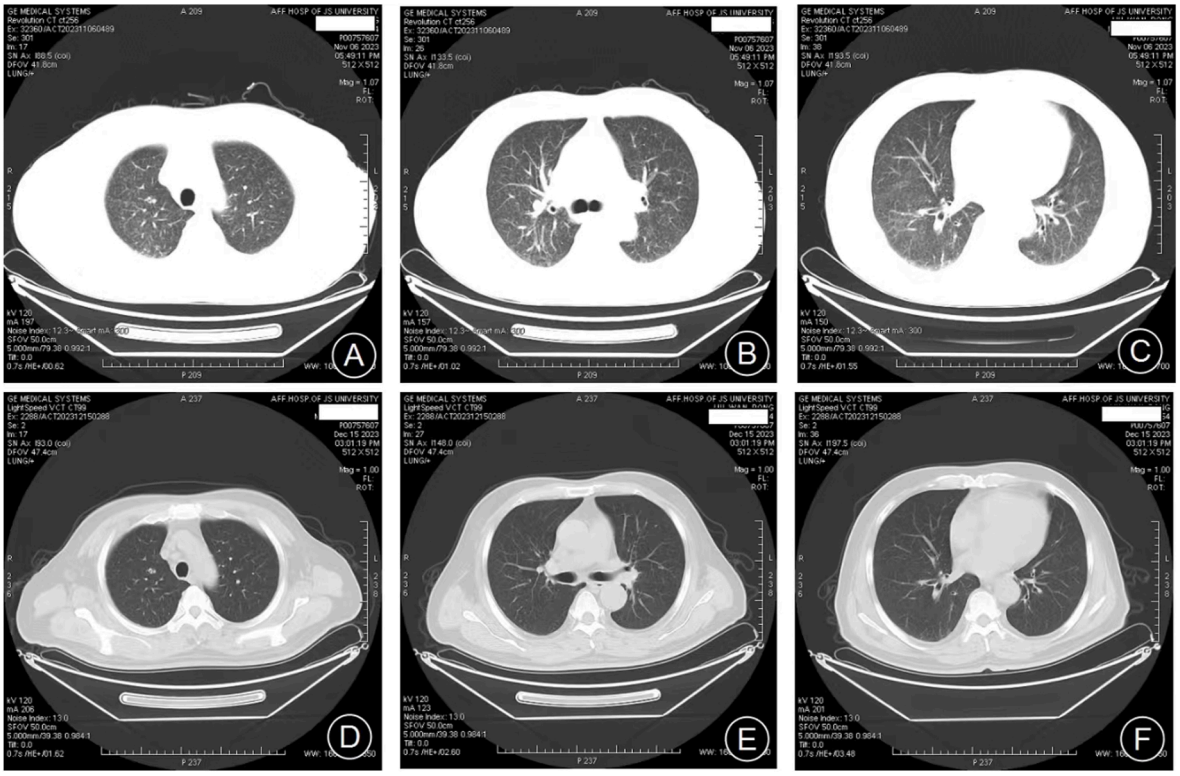

Fig. 1. The computed tomography (CT) of case one pre-treated (A–C) and pro-treated (D–F) with Voriconazole at different levels. After one-month treatment, the lesions were absorbed obviously.

tion of chest CT showed significantly decreased diffuse speck obscure shadows in both lungs compared with pre-treatment (Fig. 1B). The CBC and coagulation convention tests were normal.

2.2. Case 2

Another 48-year-old man was hospitalized with a one-week cough, fever, and respiratory failure on October 07, 2023. He had a hypertension history for five years and denied a history of coronary artery disease (CAD) and diabetes mellitus. Chest CT showed multiple specks and a patchy appearance of ground glass shadows and millary nodules in the lungs, with unclear boundaries (Fig. 2A). The white blood cell count (WBC) of 6.1 $\times$ 10^9/L, red blood cell (RBC) of 5.65 $\times$ 10^{12}/L, hemoglobin of 146g/L, platelet count/blood platelet count of 3.69 $\times$ 10^9/L, and HS-CRP of 4.7mg/L. The biochemical indicator of ALB of 39.9g/L, total cholesterol (TC) of 6.74 mmol/L, HDL-C of 0.91mmol/L, LDL-C of 4.52mmol/L, ALT of 77.4U/L, and AST of 188U/L. Carcinoembryonic antigen (CEA) of 5.91ng/mL. anti-streptolysin O (ASO) of 196.0 IU/mL. EST was 19mm/h. It is negative for the COVID-19 test. Fungal 1-3-β-D glucose was 80.00pg/mL. The galactomannan (GM) test was positive. No abnormality was observed on the anti-acid stain, Interleukin-6, autoantibodies, tuberculous infection T cell test, coagulation convention test, PCT, blood transfusion associated tests, MPO, and PR3. The blood gas indicators were measured, with pH of 7.468, PCO_2 of 40.0 mmHg, PO_2 of 91.5 mmHg, oxygen absorbent of 3L/mm, and oxygenation index of 274.5. NGS identified Whipple disease, Candida albicans, and *C albidus*. The pathology on the lung showed chronic inflammation companies stromal fibrosis, interstitial local foam tissue gathering, and local coal dust deposit in the bronchial mucosa. He was treated with antifungal drugs of voriconazole tablet with 0.2g Bid for one week. Two weeks later, the chest CT showed little inflammation in the lungs (Fig. 2B).

3. Literature review

We searched international databases (PubMed and Embase) and national databases (CNKI and WanFang Data) using keywords of “Cryptococcus albidus” and “fungemia” before June 6, 2023. We only selected the literature published after 2000 years. Total of 18 cases of *C albidus* infection cases were identified, eight of which were invasive *C albidus* infection, and ten were noninvasive infection. Only two female cases. The reports originated in the Americas, Europe, and Asia. None died cases were reported in noninvasive infection. *C albidus* infection can be happened from newborn babies to elder patients. Site of isolation are skin (n = 5), eye (n = 2), lung (n = 3), blood (n = 3), peritoneal lavage fluid (n = 1), sputum (n = 1), penile lesion (n = 1), and CSF (n = 1). Drugs of fluconazole (n = 10), AmpB (n = 8), itraconazole (n = 2), 5-FC (n = 2), caspofungin (n = 2), posaconazole (n = 1), caspofungin (n = 2), voriconazole (n = 2) were used and showed good performance.

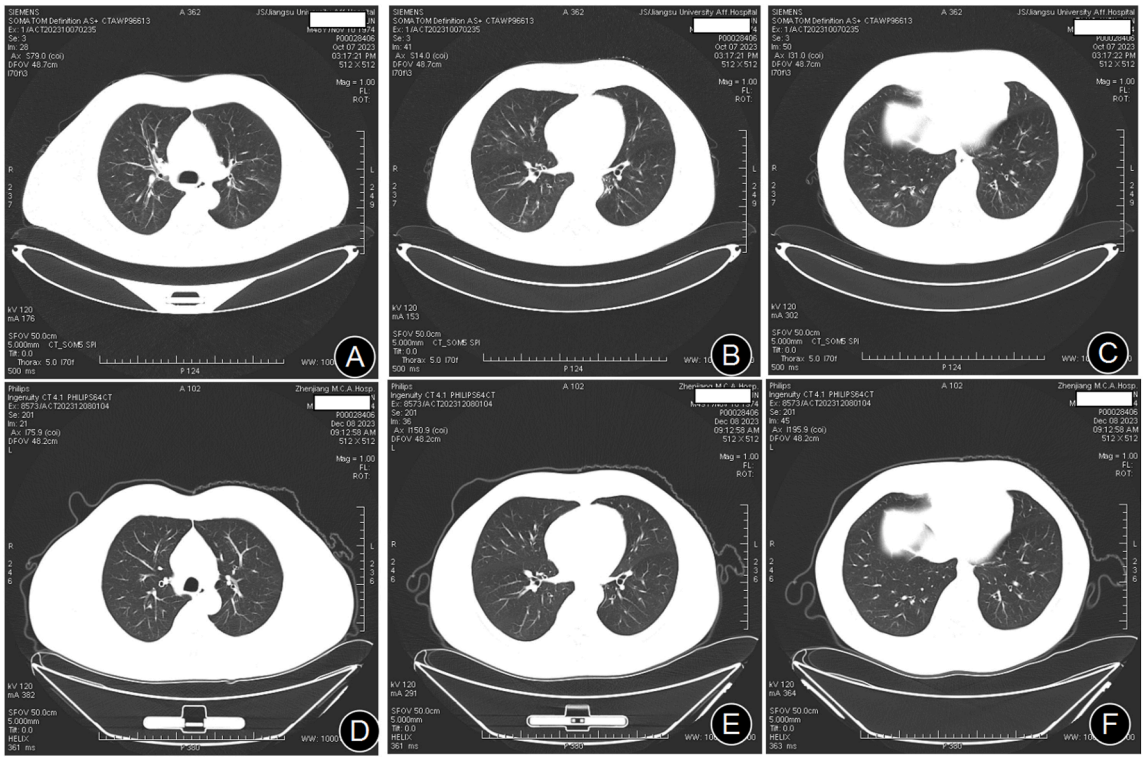

Fig. 2. The computed tomography of case two pre-treated (A–C) and pro-treated (D–F) with Voriconazole at different levels. After one-month treatment, the lesions were absorbed obviously.

4. Discussion

Two case reports revealed two patients infected with *C albidus* showing millary nodules, who were treated with antifungal drugs of voriconazole tablets, showing good performance. Cryptococcus albidus and millary nodules are all relatively rare in clinical. As reported by Choe YJ [5], there are 20 *C albidus* infections were reported, two involved in children and seven cases of noninvasive infection. Being an opportunistic yeast, *C albidus* is not life-threatening.

Combined with our present two cases, there are 18 cases were reported from 2000 years to now. The symptoms of *C albidus* infection varied. In our case reports, the symptoms of both cases are similar, showing cough and fever, which are the same as other common Cryptococcus infections. It is difficult to distinguish *C albidus* and common Cryptococcus through the symptoms. As reported, diffuse abdominal pain is also one symptom of *C albidus* [5]. Ragupathi L and Reyna M report one case with persistent severe generalized abdominal pain associated with vomiting, nausea, and inability to tolerate oral intake [6].

Fluconazole, AmpB, and itraconazole were used as antifungal drugs for noninvasive *C albidus* infection and showed good performance [7–13]. The affected anatomy was either the skin or eyes. Fluconazole, AmpB, itraconazole, 5-FC, caspofungin, posaconazole, caspofungin, and voriconazole were used as antifungal drugs for *C albidus* infection [6,14–19]. Fluconazole and AmpB were widely used. In addition, posaconazole is a successful treatment for fungemia due to *C albidus* in a liver transplant recipient [20]. However, in invasive *C albidus* infection, some of the patients died and some survived. Although the patients with invasive *C albidus* infection have accepted antifungal treatment, the overall mortality is still high [5]. The high fatality rate might be caused by underlying blood cancers, chronic immunocompromising disorders, or immunosuppressive agents. Additionally, delayed diagnosis and ineffective therapy also contribute to the poor outcome. In our two case reports, 0.2g Bid voriconazole tablet for one week can improve the clinical symptoms, showing good performance. Therefore, high efficiency and fast detection are very important, especially for invasive *C albidus* infection.

Fast and accurate diagnosis is an important prerequisite for effective treatment, condition monitoring, and control of the spread of the disease. Over the past decades, *C albidus* diagnosis mainly depends on yeast cultivation and accurate identification with biochemical methods or mass spectrometry. However, these methods need a long time and show complex processes and low sensitivity. In recent years, NGS has been widely used for its fast, accurate, and high-throughput characteristics.

5. Conclusions

Accurate microbiological diagnosis of NGS and effective therapy as antifungal treatment of voriconazole tablet are critical for *C albidus* infection.

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Availability of data and materials

The patient information and medical records used for the case report are available from the corresponding author upon request.

Ethics approval and consent to participate

This study did not include experiments on animals or humans. The patients consented to the use of their data for this case report.

Consent for publication

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

CRediT authorship contribution statement

Yikun Chen: Conceptualization, Data curation, Writing – original draft. **Lirong Zhu:** Data curation, Resources, Writing – review & editing. **Fenhong Qian:** Resources, Writing – review & editing. **Huazhong Cai:** Formal analysis, Writing – review & editing. **Jiangning Yin:** Conceptualization, Writing – review & editing.

Declaration of competing interest

None.

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