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Case report

Pulmonary cryptococcosis closely mimicking lung cancer in a membranous nephropathy patient taking calcineurin inhibitor

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ABSTRACT

In patients with membranous nephropathy (MN), malignancy may be either the underlying disease or results of immunosuppressive therapy which may also lead to opportunistic infections including the pulmonary cryptococcosis. On CT scan, nodule is the most common feature in pulmonary cryptococcosis and it can mimic lung cancer both clinically and radiologically. Therefore, pulmonary nodular lesions caused by cryptococcosis may be easily misdiagnosed and require unnecessary surgical treatment. As such, we herein presented an isolated subpleural solitary nodule with satellite lesion that closely mimicked lung cancer on both contrast-enhanced computed tomography (CT) scan and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT in an MN patient under long-term tacrolimus regimen. Cryptococcosis was ascertained by the finding of oval thick-walled yeast on histopathology of the lung biopsy specimen taken during the Argon-Helium cryotherapy. Further, the pulmonary lesions progressively dissipated after antifungal treatment. Arguably, our experience may help clinicians in general and nephrologists in particular with a better understanding of the cryptococcal infection manifesting as pulmonary nodule(s) in the MN patients and contribute to more efficacious differential diagnosis against the lung cancer.

Introduction

Pulmonary cryptococcosis is frequently seen in immunocompromised patients and has become an emerging disease in immunocompetent ones [1]. It was the third most common invasive fungal infection among the transplant recipients, accounting for 8% of the incidence [2]. Moreover, prevalence of the cryptococcal infection has increased with the application of glucocorticoids, immune-suppressants and antitumor drugs [3]. Indeed, an increasing number of non-AIDS patients have been diagnosed with pulmonary cryptococcosis in China over the last 30 years, with 57.7% of them underwent surgery [4]. On CT scan, nodule is the most common feature in pulmonary cryptococcosis and it can mimic lung cancer both clinically and radiologically [5]. Accordingly, one major concern was that pulmonary lesions caused by cryptococcosis may be easily misdiagnosed and require unnecessary surgical treatment.

This clinical scenario of similarity was under-recognized and under-reported in patients with membranous nephropathy (MN) receiving immunosuppressive therapy. In these patients, malignancy may be either the underlying disease [6] or results of immunosuppressive therapy [7], which may also lead to opportunistic infections including the pulmonary cryptococcosis [8]. As such, we herein described an isolated subpleural nodule with satellite lesion that closely mimicked lung cancer on contrast-enhanced CT scan and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (FDG-PET/CT) in an MN patient under long-term tacrolimus regimen. Cryptococcosis was determined by histopathology examination of the lung biopsy specimen collected during the Argon-Helium cryotherapy. Further, the pulmonary lesions dissipated after antifungal treatment. Arguably, our experience may help clinicians in general and nephrologists in particular with a better understanding of this kind of cryptococcal infection and make differential diagnosis against the lung cancer more efficaciously.

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Case

A 53-year-old man was referred to our hospital due to space-occupying lesions in his right lung, which was discovered at a local hospital during routine health check six months ago. Contrast-enhanced CT taken at provincial tumor hospital four months ago further confirmed a solid nodule at the right lower lobe considered as lung cancer and a smaller adjacent one that was suggestive of malignancy (Fig. 1A). Without perceptible discomfort, the patient was wavering for a therapeutic decision upon these findings until his arrival. Three years prior to this event, he had biopsy-prove MN and began the tacrolimus and methylprednisolone regime according to the KDIGO guidelines [9]. On arrival, however, he was still taking daily tacrolimus and methylprednisolone at 1.0 mg twice and 8 mg once, respectively, with adjustment of the doses *ad interim* untraceable. Otherwise, he was non-smoker and had no history of pulmonary disease.

On admission, the patient's vitals were temperature 36.1°C, pulse rate 90 beats/min, respiratory rate 20 times/min, blood pressure 145/95 mmHg, and oxygen saturation 98% on ambient air. Physical examination was unremarkable and, in particular, there was no dullness to percussion and abnormal breath sounds in the right lung zones. Initial workup found normal full blood count, liver and renal function, coagulation and electrolytes, including hemoglobin 129 g/L, plasma albumin 33.1 g/L, serum creatinine 60.2 μmol/L (reference 57.0–97.0 μmol/L) and 24-hour urinary protein excretion 5.2 g. Immunoglobulin G titer, CD4 + T lymphocyte count, fugal G- and GM-test were also normal. In addition, serum cytokeratin 19 fragment, neuron specific enolase, squamous cell carcinoma antigen and gastrin-releasing peptide precursors were all negative. Subsequently, PET-CT detected accumulation of the ^{18}FDG in the above said solid nodule with a maximum standard uptake value of approximately 12.2 and diameter of 1.7 cm (Fig. 1B) and its satellite lesion. A diagnosis of lung cancer was considered and, upon consensus of medical staffs and the patient, Argon-Helium cryotherapy was performed (Fig. 2C). Nevertheless, histopathology of the specimen obtained from both nodules revealed numerous oval-shaped, thick-walled yeast cells compatible with *Cryptococcus* spp. (Fig. 3). Hence, tacrolimus but not the corticosteroid was discontinued and fluconazole was given as recommended [10]. Follow-up CT scans at 1- and 4-month thereafter showed progressive regression of the pulmonary lesions without relapsed infection (Fig. 2D).

Discussion

Cryptococcus is a genus of encapsulated yeasts with worldwide distribution that belongs to the Basidiomycota phylum [11]. Some Cryptococcus species are pathogenic to humans and typically cause meningitis and infections in the airways, which is the most common portal of entry. Pulmonary cryptococcosis usually presents with nonspecific symptoms of cough, dyspnea, chest pain and fever [12]. However, immunocompromised patients may have a more aggressive

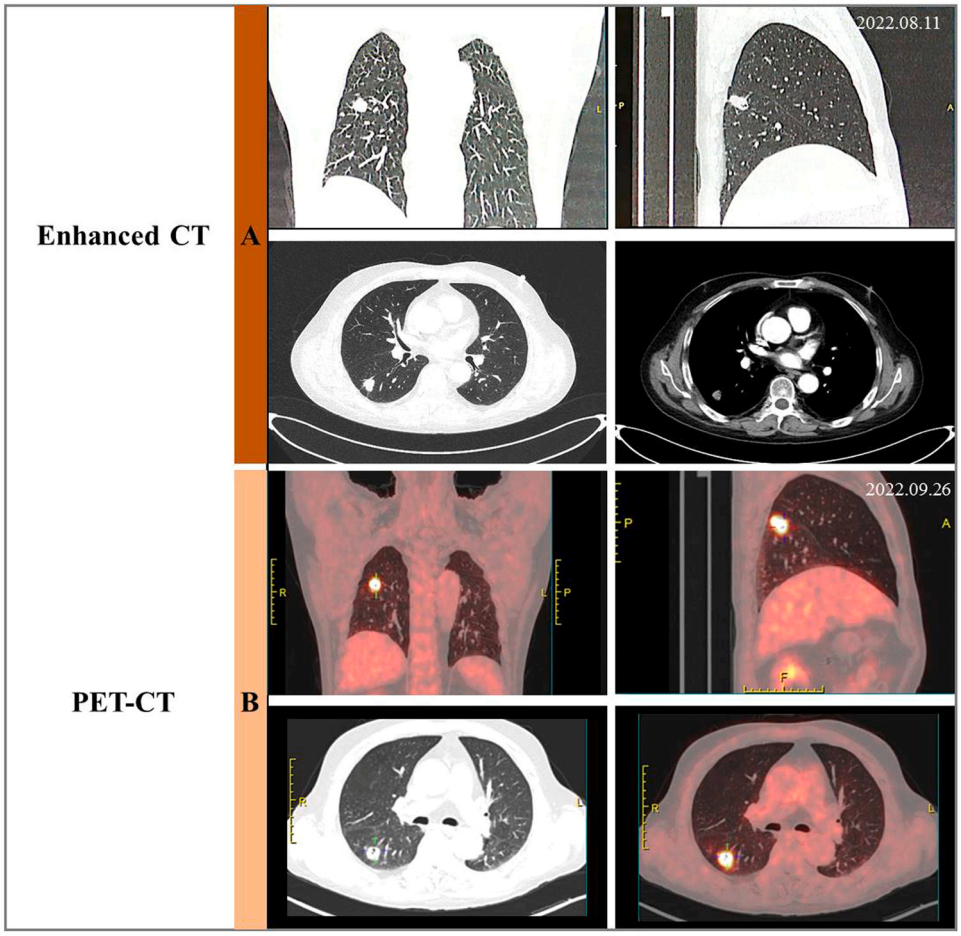

Fig. 1. Contrast-enhanced CT and PET-CT findings of the pulmonary cryptococcosis in our MN patient under long-term tacrolimus regimen. A (the dark brown bar): contrast-enhanced CT showed the isolated subpleural solidary nodule in the dorsal segment of right lower lobe. Spiculation, vacuole and pleural indentation were also visible. B (the brown bar): PET-CT showed accumulation of the ^{18}FDG in the above said nodule with a maximum standard uptake value of approximately 12.2 and diameter of 1.7 cm. The lesion appeared to be in a shallow lobular shape, with eccentric and irregular small vacuole inside. Adjacent interlobular pleura was pulled and displaced.

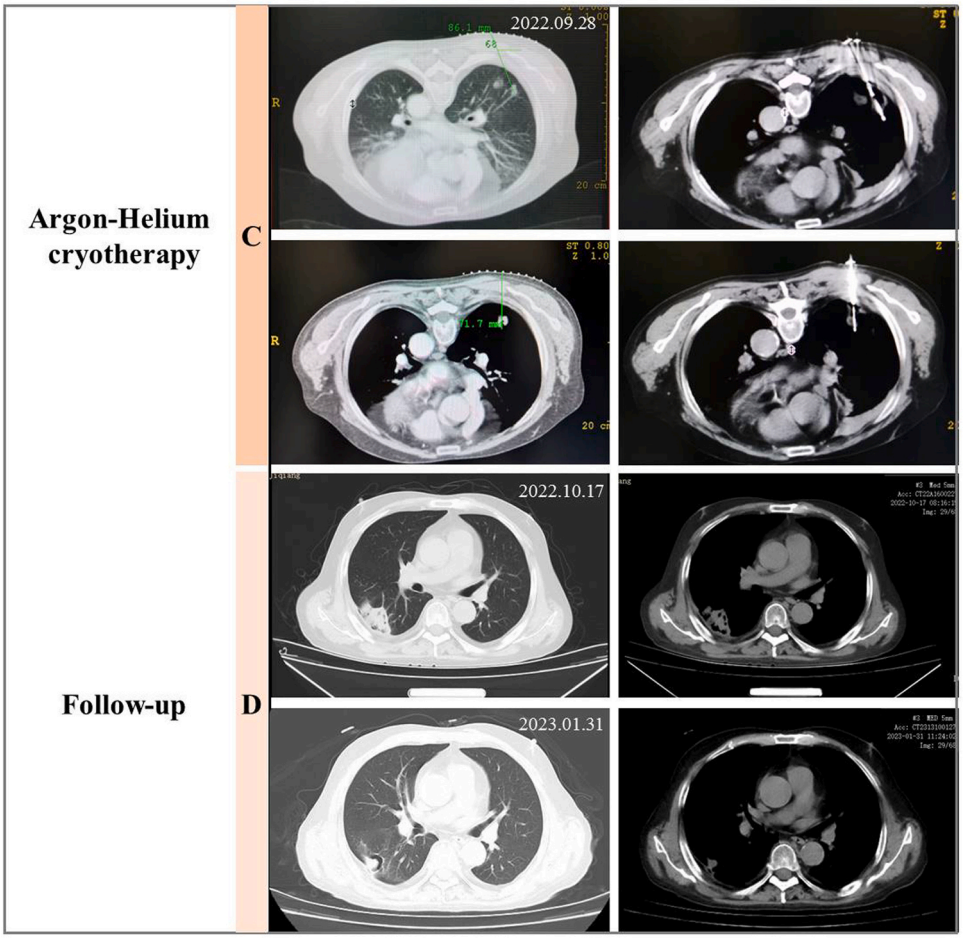

Fig. 2. Argon-Helium cryotherapy and follow-up findings of the pulmonary cryptococcosis in the MN patient. C (the light brown bar): Images taken during the Argon-Helium cryotherapy revealed the nodule and satellite lesion. D (the pale brown bar): CT scan at 1 and 4 months follow-up after initiation of the antifungal treatment. Upper panel: mass-like opacities of 5.8 × 2.7 × 0.8 cm upon unclear boundaries, with cavities inside rimmed by an irregular edge. Lower panel: irregular cavity of 4.0 × 2.2 × 0.6 cm with an uneven wall thickness and nodular protrusion inside.

disease nature. Consistently, acute respiratory failure associated with pulmonary cryptococcosis was reported in 33% of a non-AIDS cohort, most of whom had a solid organ transplant [13]. Apart from the transplantation, immunocompromised conditions also comprise of HIV infection, diabetes mellitus, malignancy and, as in our case, corticosteroid or immunosuppressive therapy [3].

Chest CT findings of pulmonary cryptococcosis can vary, but the most common ones involve solitary or multiple nodules or mass-like opacities [5]. These presentations may be related to the formation of inflammatory granulomas and fibrous tissue after phagocytosis of the cryptococci by macrophages. Furthermore, air bronchogram or vacuole, and halo sign were more commonly detected, with 81.8% of the subjects having any one of them in this report [5]. Nonetheless, signs of lobulation, spiculation, and pleural indentation were present due to uneven contraction of the fibrous tissue. As a result, incidence of isolated nodular lesion in pulmonary cryptococcosis misdiagnosed as lung cancer was higher than that in lung cancer *per se* [14]. Of note, both contrast-enhanced CT and ^{18}FDG PET-CT had limited value in differentiating these nodules because they usually exhibited enhancement and high FDG uptake in pulmonary cryptococcosis, thus mimicking malignancy [15]. In this regard, Chen et al. has proposed three conditions that single or multiple nodules should be considered as pulmonary cryptococcosis, especially in the immunocompromised patients [5].

The renal community has both witnessed and benefited from the evolution of therapeutic modality for MN, which was originally initiated from the alkylating agents, followed by the calcineurin inhibitors and currently innovated to the B-cell depletion method with rituximab and, more recently, obinutuzumab [16]. Consequently, opportunistic infections and malignancy have always been issues of close attention during immunosuppression as described in the Core Curriculum 2022 of the American Journal of Kidney Disease [17]. In this context, there are bacterial, opportunistic, and viral infections, and infection prophylaxis during immunosuppression for kidney diseases has been addressed *ad hoc* against pneumocystis jirovecii and candida. This caveat is further exemplified by the management of MN and we previously found an 8.7% incidence of pulmonary infection in the MN patients receiving the cyclosporin regimen [8]. In our work, types of the pathogen were bacteria (43.3%), fungus (24.3%), mixed (13.5%), virus (10.8%) and pneumocystis (8.1%). Precisely, pulmonary fungal infections caused by aspergillus, cryptococcus and mucor were recorded in these patients [18].

Meanwhile, MN is unique in that it is inherently related to malignancy. More specifically, the estimated prevalence of malignancy in patients with MN was 10%, with lung cancer as the top one accounting for one quarter of all cases [19]. Extra caution should be exercised since median time from diagnosis of MN to cancer in these patients was reportedly 5 years [20]. Pulmonary nodule(s) in the MN patients therefore needs more careful evaluation, with or without immunosuppression. Deciphering these enigmatic nodular lesions in the background of MN requires cross-training from nephrology, microbiology and medical imaging, which is elaborate but currently from sufficient. Our work may virtually facilitate such knowledge convergence and

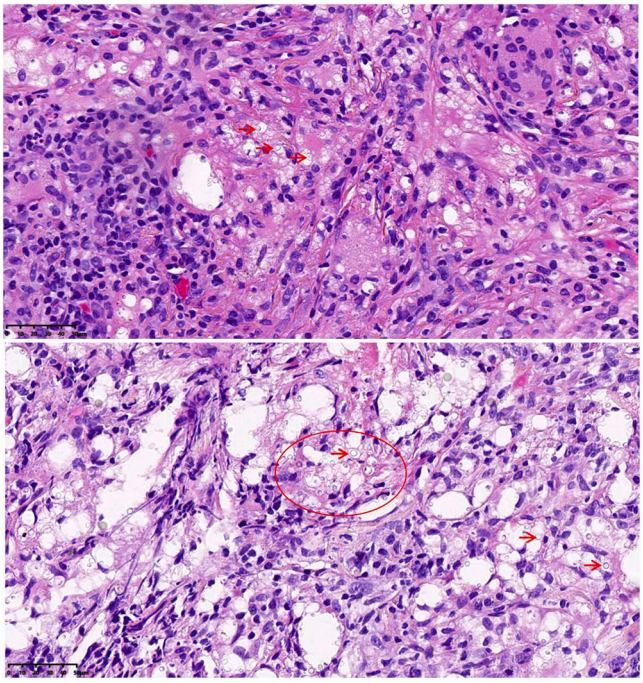

Fig. 3. Histopathology of the issues taken from both the nodule and satellite lesion during Argon-helium cryotherapy. Numerous oval-shaped, thick-walled yeast cells compatible with *Cryptococcus* spp. were visible (red arrow), upon an ostensibly chronic inflammatory background with infiltration of a large number of histiocytes. Relationship of the yeasts with alveoli was depicted in circle. There was no evidence of malignancy (HE×400).

contribute to a successful therapeutic decision.

Diagnosis of the pulmonary cryptococcosis is generally based on a combination of clinical indication, radiological suspicion and laboratory confirmation [21]. The methods used to confirm the infection are culture, direct microscopic, histopathology, serology and molecular detection. Among them, lung biopsy is believed to be the best diagnostic option and cryptococcus on histopathology examination appears as narrow-based budding yeasts (4–10 μm), usually surrounded by thick capsules in the lung tissue. Once confirmed, fluconazole is the drug of choice for patients without involvement of the central nervous system and proper antifungal therapy for pulmonary cryptococcosis was reported elsewhere in details [10].

Conclusion

We described a clinical scenario of pulmonary cryptococcosis closely mimics lung cancer on contrast-enhanced CT and PET-CT in an MN patient. Our current findings thus supported tissue confirmation, especially in immunosuppressed patients. It may help nephrologists be more familiar with this kind of nodular lesion during the treatment of MN and break pulmonary cryptococcosis out of suspected cases of lung cancer.

Consent statement

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

Ethical approval

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the Helsinki Declaration, and has been approved by the Ethics Committee of the First Hospital of HeBei Medical University (No. 20220321).

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CRediT authorship contribution statement

ZhiPeng Zhao: Treatment of the patient. **GuangWei Ren**: Data collections. **Chong Liu**: Imaging interpretation. **JianZhu Yang**: Histopathology examination. **LiHong Zhang**: Clinical coordination. **Tao Wang**: Conceptualization, Investigation, Writing the original draft, Reviewing the final edition. All authors contributed to the writing of the final manuscript and approved the version of the manuscript to be submitted.

Declaration of Generative AI and AI-assisted technologies in the writing process

None.

Declaration of Competing Interest

The authors declare none of the above said conflicts of interest.

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