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Cryptococcosis mimicking pulmonary metastasis during treatment with tamoxifen for breast cancer after surgery: A case report

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► ***Case report***

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ABSTRACT

Pulmonary cryptococcosis (PC) of the lungs is a fungal infection often occurring in immunocompromised patients, which is most commonly contracted by inhalation. Here, we report the case of a 44-year-old woman who had undergone modified radical surgery for stage I intraductal carcinoma of the left breast one year earlier and had been undergoing endocrine therapy with tamoxifen. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) findings indicated multiple pulmonary nodules, which was highly suspicious of lung metastasis from breast cancer. However, the pathological results suggested cryptococcus infection. The patient was subsequently treated with itraconazole antifungal therapy. However, a chest computed tomography (CT) examination one month later revealed that both lung lesions were still present. Her clinician suspected they were due to her intake of the estrogen receptor inhibitor tamoxifen and asked her to stop temporarily taking the drug. One month later, chest CT reexamination revealed that the lung lesions had disappeared. So far, there have been no reports of pulmonary cryptococcosis caused by tamoxifen after breast cancer surgery. Our case study suggests that PC infection may be one of the rare side effects of tamoxifen and should be considered in the differential diagnosis of multiple nodules in both lungs in patients with a history of cancer surgery and taking estrogen receptor inhibitors. Therefore, the etiology of infections should be considered in the differential diagnosis, especially in patients taking estrogen receptor inhibitors after tumor surgery.

INTRODUCTION

Pulmonary cryptococcosis (PC) is a fungal infection, whose most common route of infection is inhalation. Specifically, the inhalation of Cryptococcus neoformans and Cryptococcus gerti spores can lead to lung involvement [1]. PC can cause pulmonary lesions, fungemia, and meningitis in both immunocompromised and immunocompetent hosts [2]. Clinically, dyspnea and cough may be observed, as well as asymptomatic infections [3]. PC may be associated with various imaging findings, such as boundary-clear nodules and tumor shadowing [2]. Therefore, the diagnosis of PC is challenging, especially when presented as multiple nodules, which may be mistaken for secondary tuberculosis or pulmonary metastatic tumors [4]. Previous studies have shown that estrogen deficiency is associated with increased infections [5]. Here, we report a case of pulmonary cryptococcal infection in a patient who was initially suspected of having pulmonary metastases after treatment with an estrogen receptor inhibitor (tamoxifen) following breast cancer surgery. Later, the lesion was pathologically diagnosed as PC, but the antifungal treatment with itraconazole did not work. Notably, the lesion disappeared after the patient was ordered to stop tamoxifen intake by clinicians. The findings of our case study suggest that PC infection may be one of the rare side effects of tamoxifen, which should be considered in the differential diagnosis of multiple pulmonary nodules in patients with a history of cancer surgery and administration of estrogen receptor inhibitors.

Case description

A 44-year-old woman underwent modified radical mastectomy one year ago for stage I intraductal carcinoma of the left breast. Since the tumor was in an early stage without lymph node metastasis, no chemoradiotherapy was performed, and the patient was treated with tamoxifen for endocrine therapy after surgery. She had suffered from progressive dyspnea in the past month and had sought medical help from the local hospital, when a chest CT (Biograph 16, Siemens, Germany) examination multiple pulmonary nodules. Then, she came to our hospital for further diagnosis and treatment. Physical

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examinations revealed weakened respiratory sounds of both lungs, with no obvious positive signs. Based on the chest CT findings of the patient, ^{18}F-FDG PET/CT (Biograph mCT, Siemens, Germany) was recommended for further evaluation of the nature of the pulmonary nodules. Multiple nodules with increased radioactive uptake were detected in both lungs, with a maximum standard uptake value (SUVmax) of 9.4. The lesions were located mainly in the left-upper and the right-lower lobes, with a maximum diameter of approximately 8 mm (figure 1).

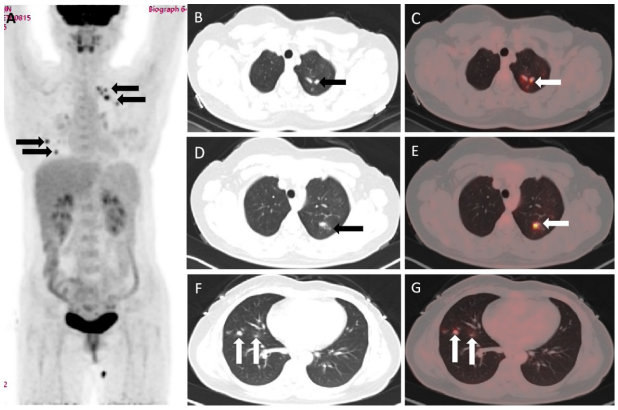


Figure 1. 18F-FDG PET/CT examination. **(A)** Whole-body MIP image shows FDG uptake nodules in the left upper lobe and right lower lobe (black arrow). **(B)** Axial chest CT showed multiple high-density nodules in the apical segment of the left upper lobe (black arrow). **(D)** Axial chest CT showing high-density nodules in the posterior segment of the left upper lobe apex (black arrow) and **(F)** Axial chest CT showing high-density nodules in the outer segment of the right lower lobe (white arrow). **(C, E and G)** Chest PET/CT fusion image showed multiple pulmonary nodules with increased radioactive uptake and SUVmax of 9.4 (white arrow). MIP, maximum intensity projection; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; SUVmax, maximum standard uptake.

Laboratory test values, including total white blood cell count, differential white blood cell count, renal and liver function tests, CRE protein, and erythrocyte sedimentation rate were within normal limits. Tests were negative for anti-HIV antibodies; the T- and B-lymphocyte levels were also normal. Based on the findings of the imaging and laboratory examinations, the patient was considered to have lung metastasis of breast cancer. She was suggested and accepted lesion biopsy under CT guidance. The pathological biopsy results (hematoxylin-eosin staining reagent, MXB Biotechnologies, Fuzhou, China) showed new cryptococcus engulfed by macrophages, surrounded by a large number of infiltrating lymphocytes and a large amount of fibrous tissue, with formation of multi-core macrophages or granuloma (figure 2).

Based on these findings, the patient was diagnosed with PC. She was subsequently treated with itraconazole for antifungal therapy. A month later, a chest CT examination revealed that the lesions in both lungs were still present. Her clinician suspected that the lesions were caused by the intake of tamoxifen (Yangzijiang Pharmaceutical Collection Co. LTD), so she was asked to stop taking tamoxifen for a month before reexamination. Surprisingly, the chest CT examination one month later showed that the lesions in the lungs had disappeared (figure 3). There was no evidence of recurrence of cryptococcosis in the two-year follow-up period.

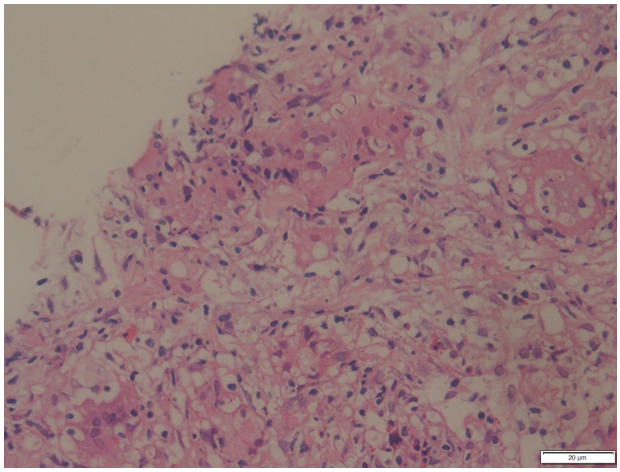


Figure 2. Histopathological findings (Hematoxylin-eosin staining: ×400) show Cryptococcus pneumonias phagocytosed by macrophages, surrounded by a large number of infiltrating lymphocytes and a large amount of fibrous tissue, forming multinucleated macrophages or granulomas.

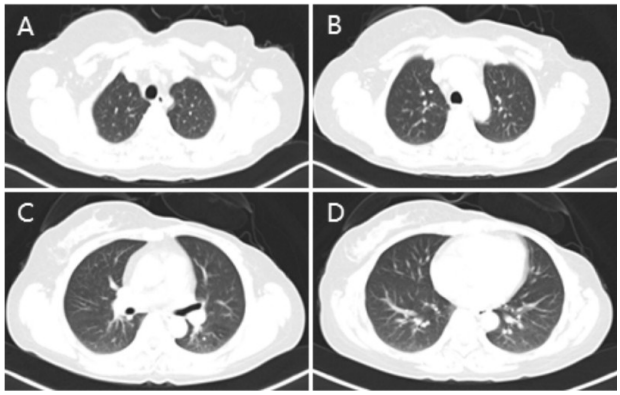


Figure 3. One month after the patient stopped taking tamoxifen, chest CT showed that the multiple nodules in both lungs disappeared.

DISCUSSION

PC is a fungal infection, whose most common route of infection is inhalation. More specifically, the inhalation of Cryptococcus neoformans and Cryptococcus gerti spores can lead to lung involvement [1]. PC is particularly common in immunocompromised hosts and is prevalent in patients with cell-mediated immune disorders, such as acquired immunodeficiency syndrome, transplant-related immunosuppression, corticosteroid therapy, chemotherapy, and neoplastic and

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lymphoproliferative diseases [6]. The clinical manifestations of PC are highly variable and influenced by the host immune status. Typical clinical symptoms include cough, fever, chest pain, and dyspnea, but the diagnosis in some cases is delayed, or they are misdiagnosed due to the lack of typical symptoms [7]. Breast cancer is a typical hormone-dependent tumor. Hence, endocrine therapies have been widely applied for the treatment of breast cancer. Selective estrogen receptor modulators (SERMs) such as tamoxifen inhibit the growth of estrogen-dependent breast cancer tumors [8]. Previous studies have shown that estrogen affects the function of the immune system and to significantly attenuate the release of proinflammatory mediators, such as tumor necrosis factor-alpha, interleukin (IL)-1β, and IL-6 from neutrophils and macrophages in rats, mice, and humans [9]. In particular, estrogen has been clearly shown to interact with nuclear factor-kappa B signaling to limit inflammatory activity. There is also growing evidence for the role of hormones in regulating anti-inflammatory/pro-lytic protein annexin A1 secretion [10]. In addition, estrogen has been reported to inhibit the growth of Cryptococcus neoformans *in-vitro* [6]. Our patient developed PC after taking tamoxifen for a long time (one year). Thus, we speculate that the cause may be estrogen deficiency due to the intake of this estrogen receptor inhibitor, which plays an important role in the regulation of the immune system by inducing direct effects on a variety of cell types [11].

The radiological findings of PC can be similar to those of other diseases and are lacking specificity, in contrast to other lung infections caused by bacteria, mycobacteria, parasites, or viruses as well as malignancies and infarctions [12]. Therefore, the probability of misdiagnosis or late diagnosis is increased due to the lack of knowledge on the typical etiology and manifestations of this disease. The "halo sign" was first used by Kuhlman *et al.*[13] to describe the appearance of hemorrhagic nodules in invasive aspergillosis. In some patients with nodular disease, ground-glass shadows appear near or around nodules, which are consistent with halo signs [14]. The diagnosis of PC is complex, usually based on a combination of clinical, radiological, and laboratory test results [15]. ^{18}F-FDG PET/CT has been widely applied in the diagnosis, staging, and post-treatment evaluation of cancer, which provides functional and anatomical information, helping to differentiate between malignant and benign lung lesions at the same time. ^{18}F-FDG PET/CT scanning findings of PC and tuberculoma are similar to those of primary and metastatic lung cancer, which leads to PC and tuberculoma misdiagnosis as metastatic tumor in patients after cancer surgery. Hence, the implementation of ^{18}F-FDG PET/CT imaging combined with SUV was recommended for semi-quantitative evaluation for identification of the nature of pulmonary nodules [16]. Reportedly, 88% of patients with PC have high FDG uptake on PET/CT scans, with a maximum standardized uptake value (SUV) between 1.4 and 13.0 [17]. Therefore, when fluorodeoxyglucose (FDG) positron emission tomography (PET) is used to distinguish infection from malignancy in multiple pulmonary nodules, potential interpretation deficiencies should be considered, especially in areas with a high prevalence of granulomatous infection and in immunocompromised patients [18]. The clinical and imaging manifestations of nodular PC lack specificity and are complex and variable, which is easy to be misdiagnosed as pulmonary tuberculosis, peripheral lung cancer, inflammatory pseudotumor, lung metastasis, etc. Percutaneous lung biopsy is the gold standard for the diagnosis of PC. Histological examinations and tissue sampling are important auxiliary diagnostic methods. HE staining (hematoxylin-eosin staining) can detect cryptococcus, fungal cell walls, and melanin; however, specific polysaccharide capsule staining may be more helpful [19]. Fluconazole is the drug of choice for PC treatment. If fluconazole is not available or a drug allergy reaction occurs, voriconazole or itraconazole may be used as an alternative treatment [1]. The prognosis of PC is good, with a significant therapeutic effect. Our patient underwent a chest CT scan examinatio0n one month after discontinuation of tamoxifen, which revealed the disappearance of lung lesions. There was no recurrence during the follow-up period of two years.

In conclusion, our patient's lung lesions disappeared after her tamoxifen intake was terminated, suggesting that PC infection may be one of the rare side effects of tamoxifen therapy. In addition, our case study provides insights into the differential diagnosis of multiple pulmonary nodules. PC should be considered as one of the differential diagnoses between metastasis and tuberculosis when multiple nodules or masses are found on ^{18}F-FDG PET/CT scan images, especially in patients taking estrogen receptor inhibitors after a history of cancer surgery.

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***Conflict of Interest*:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

***Ethics approval and consent to participate*:** This study was conducted under the standards of the Ethics Committee of the Affiliated Hospital of Zunyi Medical University, Zunyi, China (Approval Number ZYFY202008of January 1, 2022). Written informed consent was obtained from the patient.

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***Data availability statement*:** The data involved in the article can be obtained through the corresponding author under reasonable conditions.

***Author contributions*:** JC was involved in funding acquisition. DL prepared the methodology and performed the investigation. HH and XH wrote the original draft version of the manuscript. XH and JC conducted review and editing of the final version of the manuscript.

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