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CASE REPORT

Asymptomatic pulmonary nodules in a patient with early-stage breast cancer: Cryptococcus infection

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Summary In breast cancer patients, pulmonary nodules are frequently considered a metastatic disease or primary lung tumor. We report the case of a 53-year-old woman with early-stage breast cancer (T1micN0M0) presenting with asymptomatic pulmonary nodules in the left upper lobe at follow-up 6 years after she underwent a mastectomy. A presumptive diagnosis of pulmonary metastasis was made, and the patient underwent a video-assisted thoracoscopic lung biopsy. Pathology showed granulomatous inflammation with Cryptococcus infection. Subsequently, antifungal therapy was prescribed, and full recovery followed. We demonstrate the importance of differentiating between pulmonary Cryptococcus infection and metastasis in breast cancer patients for correct management. The relationship between pulmonary Cryptococcus infection and breast cancer is also discussed.

Introduction

Pulmonary nodules in patients with breast cancer can be diagnosed as a variant disease. If the patient presents with a solitary pulmonary nodule, primary lung tumor is the most common diagnosis.[1—4] In contrast, multiple nodules are considered metastatic lesions rather than a primary lung tumor.[3,4] However, breast cancer patients with pulmonary nodules presenting with an inflammatory reaction and infection are uncommon.

Pulmonary cryptococcosis is a rare infection and may be lethal in an immunocompromised patient. It is important for clinicians to differentiate between pulmonary cryptococcosis and malignant pulmonary nodules in breast cancer patients. We describe a rare case of asymptomatic pulmonary cryptococcosis in an early-stage breast cancer patient. Correct diagnosis and treatment resulted in a favorable outcome.

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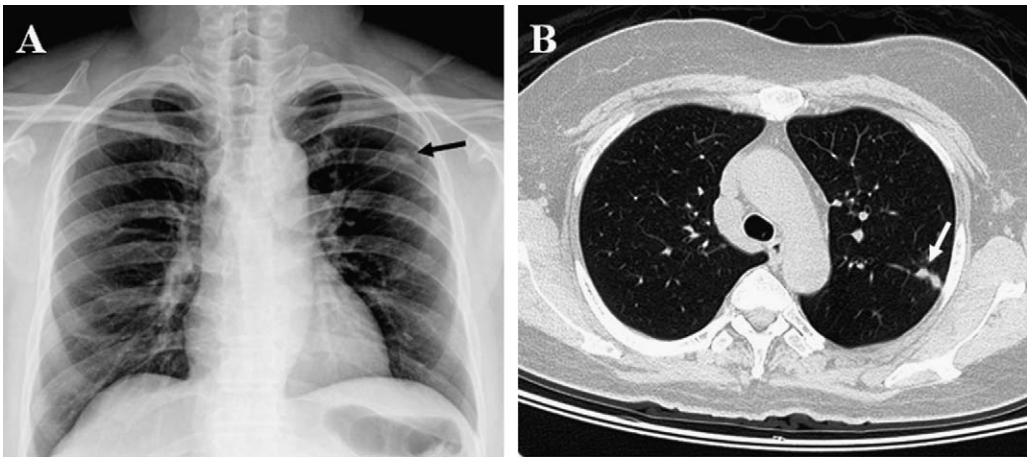

Figure 1 A Chest radiography showing several nodular opacities (black arrow) in the periphery of the left upper lung. (B) Computed tomography of the chest showing multiple partially ill-defined, soft-tissue nodules (white arrow) in the peripheral region of the left upper lung.

Case report

A 53-year-old woman with left-sided breast cancer had undergone a modified radical mastectomy with immediate breast reconstruction 6 years ago. Pathological examination had revealed intraductal carcinoma with microinvasion, and the oncology work-up revealed T1micN0M0, grade II, stage I disease. The tumor expressed estrogen and progesterone receptors without HER-2/neu overexpression. Following surgery, the patient received only hormone therapy with tamoxifen for 5 years. There was no recurrence or metastasis of breast carcinoma at follow-up for 5 years. During follow-up at 6 years, chest radiography (Figure 1A) revealed multiple nodular opacities in the peripheral region of the left lung. The patient had no associated symptoms such as fever, productive cough, or chest pain. Laboratory investigations revealed a white blood cell count of 4.1×10^9/l, with 51.9% segmented neutrophils. The levels of the tumor markers CEA and CA153 were within normal limits. Ultrasonography of the breast and mammography revealed no evidence of recurrence. Computed tomography (CT) of the chest (Figure 1B) revealed multiple partially well-defined, soft-tissue nodules in the peripheral region of the left upper lung; the largest was 1.2×0.6 cm in size.

In our breast cancer patient with multiple pulmonary nodules, the possibility of pulmonary metastasis was considered. Subsequently, she underwent a video-assisted thoracoscopic lung biopsy. The pathology (Figure 2A) revealed a chronic granulomatous inflammatory lesion consistent with many yeast-form fungi encapsulated within epithelioid cells. Special staining with mucicarmine confirmed Cryptococcus infection (Figure 2B). Later, the serology test for Cryptococcus antigen was found to be positive, with a titer of 1:32; no HIV antibodies were detected. We did not examine the cerebrospinal fluid because of the low titer of the Cryptococcus antigen and the absence of symptoms of central nervous system (CNS) infection. The patient received antifungal therapy with fluconazole for 3 months. Two months after the treatment, the serum Cryptococcus antigen titer decreased to 1:8. No additional respiratory symptoms devel-

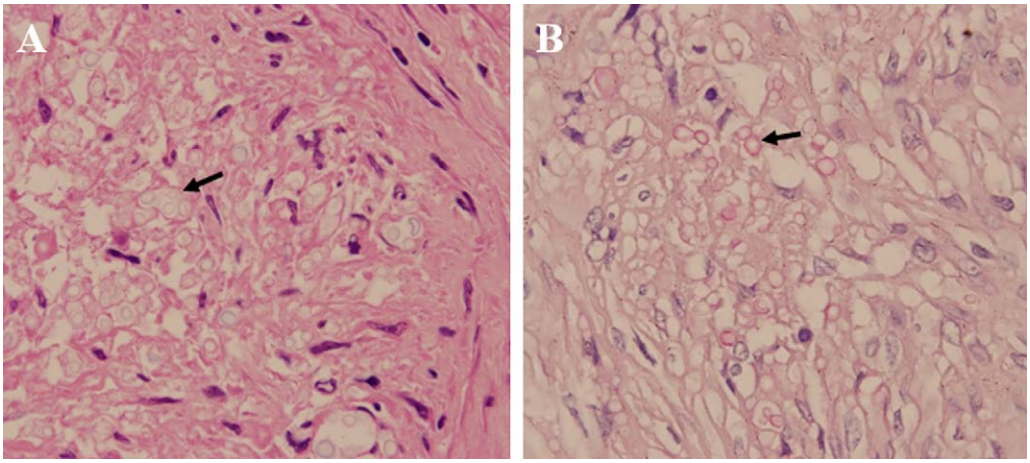

Figure 2 A Many yeast-form fungi with capsules (arrow) were identified within the epithelioid cells (hematoxylin and eosin stain, ×400). (B) Encapsulated forms of Cryptococcus (arrow) were demonstrated by mucicarmine stain (×400).

oped, and the patient's chest radiograph returned to normal, except for several tiny surgical scars that could be observed on the radiograph.

Discussion

Differentiating between a benign lesion and primary tumor or metastasis in patients with pulmonary nodules is crucial for clinicians and is difficult in some patients such as cancer patients. Surgical resection is the only recommended treatment for early-stage non-small cell lung cancer. Breast cancer patients with multiple pulmonary nodules may be regarded as having metastatic disease and may be treated immediately with chemotherapy. However, according to the literature, 5—18% of breast cancer patients with multiple pulmonary nodules have been found to have non-malignant disease according to the results of tissue biopsy.[1,2,4,5] Thus, it is important that a biopsy be performed for definite diagnosis and correct management.

Cryptococcus infection is an opportunistic infection that predominantly affects immunocompromised patients. HIV infection is a well-documented major risk factor for Cryptococcus infection.[6] Idiopathic CD4 lymphocytopenia (ICL) is characterized by CD4 T-cell depletion in the absence of HIV infection, and a few cases with Cryptococcus infection have been reported in recent years. Unlike HIV infection, the decline in the CD4 cell counts of patients with ICL is often slow. The clinical presentation of ICL ranges from an asymptomatic laboratory abnormality to life-threatening opportunistic infection.[7]

In fact, it seems that a large proportion of the population has been exposed to this fungus, and the subsequent course of infection is mainly determined by the immune status of the individual.[8] In immunocompromised patients, disease progression is often rapid and severe. Our patient only received hormone therapy with tamoxifen for 5 years after surgery. She exhibited mild leukopenia, and this may have weakened the defense mechanism against Cryptococcus infection. Leukopenia has been reported during tamoxifen therapy but is uncommon, and the white cell count will return to the normal range in most patients within a few weeks of stopping treatment.[8,9]

Approximately one-third of immunocompetent patients with Cryptococcus infection are asymptomatic, and the most common symptoms are cough, dyspnea, and fever.[10,11] In asymptomatic patients, the pulmonary infection is usually discovered incidentally following chest radiography. Infiltration lesions, partial or well-defined margins, and non-calcified nodules or masses are common, while cavity-like lesions are less frequently observed but more commonly seen on the chest radiograph of immunocompromised patients.[12,13] Cryptococcus infection of the CNS is dramatically higher in immunocompromised patients. It is a critical to note that at the time of diagnosis of pulmonary cryptococcal infection, 90% of HIV/AIDS patients can already have CNS cryptococcosis.[11] However, in immunocompetent patients with pulmonary Cryptococcus infection, subsequent dissemination to the CNS is infrequent after appropriate treatment.[12] Lumbar puncture is not always necessary for an immunocompetent patient with pulmonary cryptococcosis; the exception is patients whose clinical condition worsens, those who present with the neurologic signs of disease progression, or those with a high serum Cryptococcus antigen titer (>1:250) in the initial work-up. None of these findings was observed in our patient, hence lumbar puncture was not performed. Furthermore, the high titer of serum Cryptococcus antigen is a characteristic of Cryptococcus infection in immunocompromised patients.[14]

A non-malignant diagnosis in breast cancer patients with pulmonary nodules is uncommon, and the differential diagnoses should include histoplasmosis, tuberculosis, cryptococcosis, and harmatoma. However, Cryptococcus infection is rare in this patient group. Once pulmonary cryptococcosis is confirmed, the patient should be treated promptly with antifungal therapy. The majority of patients respond well to this treatment.

Kontoyiannis et al. studied 31 cancer patients with cryptococcosis, including 19 with pulmonary cryptococcosis, and none of them had been correctly diagnosed before tissue biopsy or serum culture.[15] Therefore, multiple pulmonary nodules in breast cancer patients may not always be lung metastases, such as in our case. Only clinical image evaluation and occasionally pathologic diagnosis can help clinicians diagnose correctly so that appropriate treatment is administered.

In patients with early-stage breast cancer, as in our case, image examinations, including CT scans, may show a suspicious inflammatory process or metastatic lesions. Breast surgeons face the choice of further chemotherapy or alternatives. We suggest that such patients undergo video-assisted thoracoscopic surgery for tissue diagnosis since this procedure is safe and not invasive. It can take out more tissue than CT-guided aspiration cytology, to make a more accurate diagnosis.

In conclusion, we present the case of a breast cancer patient with multiple pulmonary nodules who underwent video-assisted thoracoscopic surgery with lung biopsy to confirm the diagnosis of Cryptococcus infection. Differentiating between pulmonary Cryptococcus infection and metastasis in breast cancer patients is important for correct management.

Conflict of interest: No conflict of interest to declare.

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