

# Late distant recurrence of breast carcinoma and metastasis to the main bronchus and choroid

## A case report

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### Abstract

**Rationale:** Metastases of breast carcinoma to the main bronchus and choroid are rare, but have been reported in relevant literature. Late distant recurrence of breast carcinoma after more than 20 years is extremely rare. Herein, we report a 57-year-old woman with late distant recurrence and metastasis to the main bronchus and choroid almost 28 years after surgery.

**Patient concerns:** At the age of 29, the patient underwent chemotherapy and endocrine treatment after a right side mastectomy to remove breast carcinoma. The patient was hospitalized for a cough with blood-tinged sputum, dysphagia, and blurred vision in the left eye at the age of 57.

**Diagnoses:** On evaluation, laboratory findings detected the elevated serum tumor markers of CA12-5, CA15-3, NSE, and Cyfra21-1. The imaging showed left lung metastase, multiple lymph node metastases, and small suspected metastases in the both sides of parietal lobes. Fundus fluorescein angiography showed choroidal occupying lesion of the left side which indicates secondary metastasis and retinal detachment. Combined with the pathological finding via fiberoptic bronchoscopic biopsy, the patient was clinically diagnosed with a late distant recurrence of breast carcinoma.

**Interventions:** The patient received oral endocrine therapy of letrozole, but she refused chemotherapy, radiotherapy and other topical treatments.

**Outcomes:** At the 3-month follow-up visit, the multiple lesions of the left lung and lymph nodes had partially regressed, and the lesion of right parietal lobe had disappeared. The patient's clinical symptoms, such as blood-tinged sputum and dysphagia, had significantly improved.

**Lessons:** We have described this case and reviewed the relevant literature concerning late distant recurrence of breast carcinoma. Importantly, this case indicates that patients with HR positive breast carcinoma are more likely to develop late distant recurrence and clinicians should not ignore the follow-up examinations even more than 20 years after the surgery.

**Abbreviations:** BC = breast carcinoma, BM = bronchial metastasis, CM = choroidal metastasis, CT = computed tomography, HR = hormone receptor, IHC = immunohistochemistry, MRI = magnetic resonance image.

**Keywords:** breast carcinoma, choroidal metastases, distant recurrence, late recurrence, main bronchus metastases

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## 1. Introduction

Breast carcinoma (BC) is one of the major malignant tumors threatening the health of women worldwide, ranking first in terms of morbidity and mortality.<sup>[1]</sup> The prognosis of early BC patients is optimistic, with a 15-year survival rate of 78%. However, patients who have been diagnosed with BC still have a risk of recurrence, even after successful surgery and adjuvant therapy. The rate of local recurrence and distant metastasis has been reported to be up to 35% within the first 10 years after surgery.<sup>[2]</sup> The risk of recurrence is typically limited to the first 5 years after diagnosis, with the recurrence rate declining rapidly thereafter. Hormone receptor (HR) positive BC patients are at risk of recurrence even after undergoing 5 years of tamoxifen treatment.<sup>[3]</sup> The most common sites of distant metastasis are the lung, bone, liver, and brain. Choroidal metastasis (CM) and main bronchial metastasis (BM) are rare. Here, we report a patient with late distant recurrence of BC and metastasis to the main bronchus and choroid almost 28 years after surgery.

## 2. Case representation

A 57-year-old woman, who underwent a mastectomy 28 years prior, was hospitalized for cough with blood-tinged sputum, dysphagia,

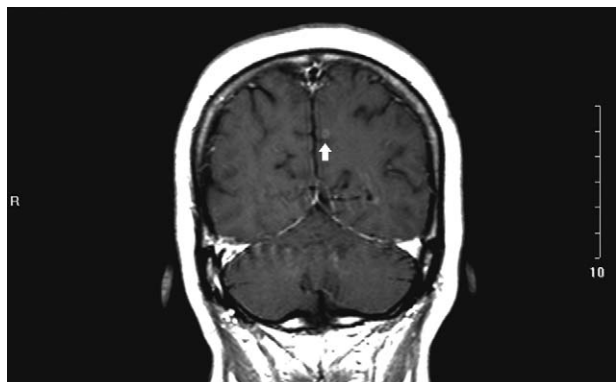


**Figure 1.** The initial computed tomography (CT) showing multiple metastases of the left lung. CT=computed tomography.

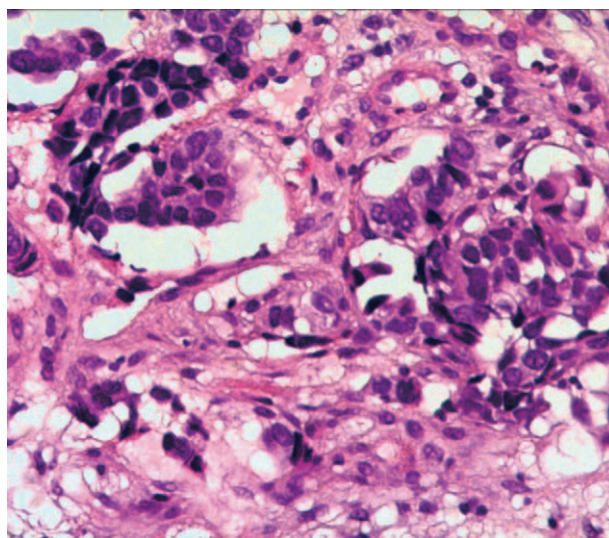
and blurred vision in the left eye on April 25, 2017. The postoperative pathological report from her initial surgery in 1989 indicated invasive ductal breast carcinoma on the right side. The tumor size was 5 cm × 5 cm without invasion of the nipple, but with 3 out of 9 axillary lymph nodes testing positive. The TNM stage was diagnosed as pT3N1M0 Stage III. The immunohistochemistry (IHC) results indicated that the tumor was estrogen receptor (ER) (+) and progesterone receptor (PR) (–). The HER-2, Ki-67, and histological grade statuses were unknown. The patient received 6 cycles of CMF chemotherapy and 2 years of endocrine treatment after surgery. There was no family history of cancer.

The thoracic and abdominal contrast-enhanced computed tomography (CT) scans performed in April of 2017 indicated lung metastase of the lower lobe in the left lung and lymph node metastases of left hilar, axillary, and mediastinal, accompanied with esophageal invasion (Fig. 1). The brain magnetic resonance image (MRI) showed small suspected metastases in both sides of parietal lobes (Fig. 2). Of the tumor markers tested, CA12-5 was 192.8 U/mL, CA15-3 was 53.09 U/mL, NSE was 20.16 ng/mL, and Cyfra21-1 was 13.52 ng/mL.

The fiberoptic bronchoscopic biopsy performed on May 12 showed moderately differentiated adenocarcinoma in the left main bronchus. The IHC results further confirmed that the primary source was invasive ductal breast carcinoma grade II (Fig. 3). It indicated that ER (+++) almost 80% strong positive cells, PR (+) almost 10% strong positive cells, HER-2 (+), Ki-67



**Figure 2.** Suspected metastasis of left parietal lobe on magnetic resonance image (arrow).



**Figure 3.** Histological examination of pulmonary biopsy with hematoxylin-eosin (HE) staining (×100). HE=hematoxylin-eosin.

(50% +), NapsinA (–), thyroid transcription factor-1 (–), P53 (–), and P63 (–) (Fig. 4). The ophthalmologic examination revealed that the visual acuities were 0.9 (right) and 0.1 (left). The anterior segments of both eyes were found to be normal, but the lenses of both eyes were turbid (the posterior capsules were prominent). A fundusoscopic examination through small pupils indicated nasal exudative lesions visible below in the left eye. Above the subretinal space, we found visible yellow red eminence lesions and a retinal wheel shaped uplift. The fundus fluorescein angiography conducted on June, 12 showed choroidal occupying lesion of left side, indicating secondary metastasis and retinal detachment (Fig. 5). The patient was clinically diagnosed with late distant recurrence of BC.

The patient refused chemotherapy, radiotherapy, and other topical treatments such as esophageal stent implantation. She received oral endocrine therapy of letrozole (2.5 mg orally once daily). A thoracic contrast-enhanced CT scan performed on August 14, 2017 showed that the multiple lesions in the left lung and the left axillary, mediastinum, and the left hilar lymph node metastases had partially regressed (Fig. 6). The brain MRI demonstrated that the size of the left parietal lobe lesion had not changed, but the right parietal lobe lesion had disappeared (Fig. 7). The patient's clinical symptoms, such as blood-tinged sputum and dysphagia, had significantly improved. The blurred vision in her left eye had slightly improved. We therefore recommended that she continue endocrine therapy.

### 3. Ethical approval

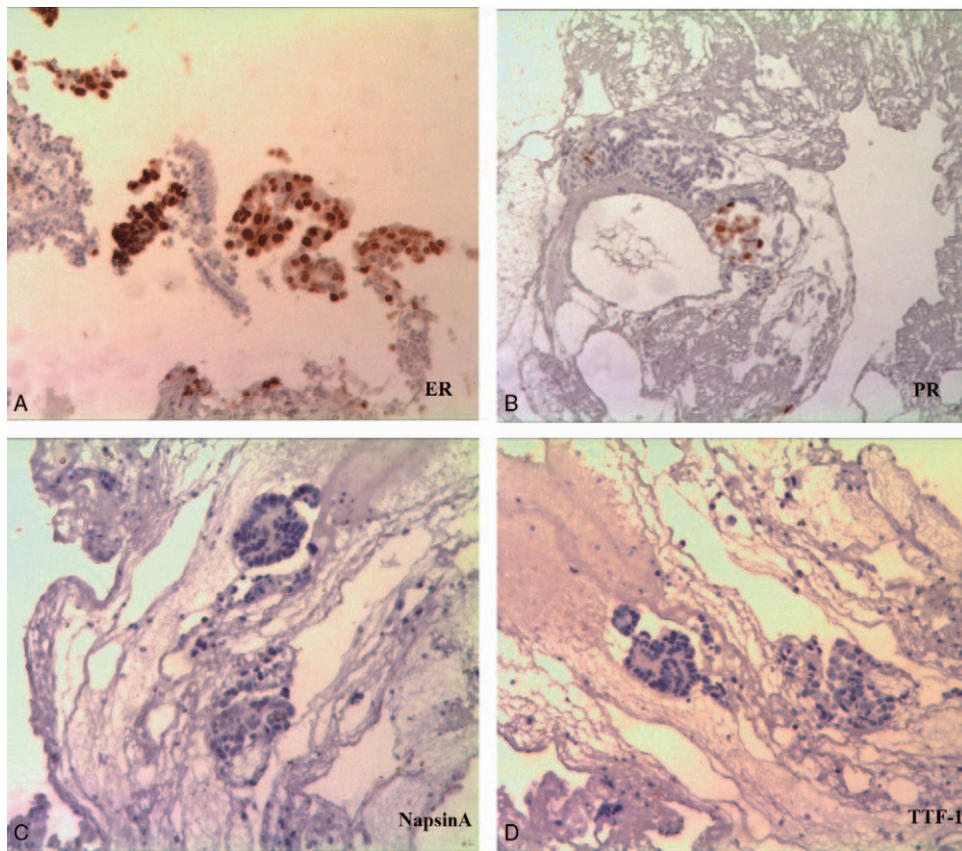
Ethical approval was not necessary because our study is a case report.

### 4. Patient approval

This patient signed an informed consent before publication.

### 5. Discussion

With the high heterogeneity of BC, individualized treatments have attracted increasing attention. A retrospective analysis



**Figure 4.** Immunohistochemical (IHC) pictures showing the positive expression of ER and PR, and negative expression of NapsinA and TTF-1. (A) ER, (B) PR, (C) NapsinA, (D) TTF-1 (x100). ER=estrogen receptor, IHC=immunohistochemical, PR=progesterone receptor, TTF-1=thyroid transcription factor-1.

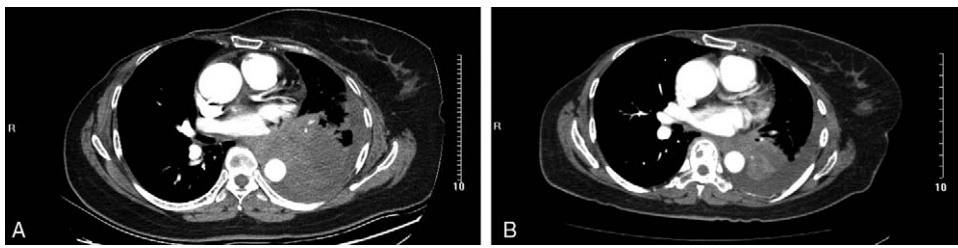
showed that the recurrence rates of stage II BC 10 and 15 years after diagnosis were 13% and 21%. Stage III BC showed 10 and 15 year recurrence rates of 18% and 30%, respectively.<sup>[4]</sup> Until now, the mechanisms of late distant recurrence have remained unknown. It is not clear whether they are caused by the intrinsic biological behaviors of tumor cells, host-driven factors, or a combination of both.<sup>[5]</sup> In recent years, some studies have suggested that tumor size, staging, IHC4, and 21-gene RS (Recurrence Score) can be used for the assessment of early recurrence risk. Nevertheless, these methods are not accurate for

the prediction of late recurrence. Lymph node status, ROR score (Risk of Recurrence), BCI (The Breast Cancer Index), and EP (the Endopredict) are all useful for the prediction of late recurrence.<sup>[6,7]</sup> The evaluation of recurrence risk in high-risk groups is necessary, in order to select certain patients in which to prolong the endocrine therapy, thereby reducing the risk of late recurrence and metastasis.

Choroidal metastasis (CM) is the most common intraocular malignant tumor, accounting for 81% to 88% of metastatic carcinomas of the eye. This may be related to the abundant blood



**Figure 5.** Exudative choroid lesions (arrow) in the left eye with exudative retinal detachment (A) fundus fluorescein angiography, (B) fundus photograph, (C) ultrasound.

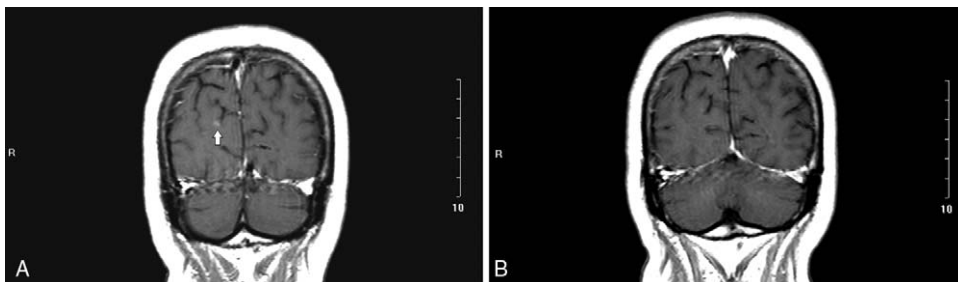


**Figure 6.** CT showing the tumor shrinkage of the left lung before (A) and after (B) endocrine therapy. CT=computed tomography.

flow of the choroid, allowing easy access to the tumor thrombus.<sup>[8,9]</sup> The most common carcinomas leading to CM are from breast cancer, accounting for 40% to 54%, followed by lung cancer, accounting for 14% to 30%. CM is a special type of breast carcinoma with multiple metastases usually occurring 2 to 4 years after diagnosis.<sup>[10]</sup> Breast carcinoma with delayed choroidal metastasis is rare and the case we reported, in which the patient was diagnosed almost 28 years after radical mastectomy, is a very rare event. Usually characterized by blurred or decreased vision, CM is often accompanied by retinal detachment and can give rise to a rapid deterioration. CM patients often suffer from headaches and pain of eye. The incidence of CM on the left side is much higher than on the right. This may mainly be due to the direct divergence of the left carotid artery from the aortic arch. The tumor embolus can therefore enter the left eye artery through the left carotid artery, while access to the right side has to go through the innominate artery. CM is reportedly related to the molecular subtype of BC. By comparing 18 patients of BC with CM and 40 patients of BC without CM, Parrozzani et al<sup>[11]</sup> suggested that the expressions of PR and ER may, to some extent, be related to the incidence of CM from BC, especially the luminal B molecular subtype. Colleoni et al<sup>[12]</sup> reported that patients with HR positive cancer, especially ER positive, had a relatively good prognosis, while they are more likely to be found with metastasis. The patient we reported with ER positive status was classified as luminal B, which was consistent with the previous findings. It is worth noting that the incidence rate of ocular metastasis seems to show an increasing trend after diagnosis of CNS metastasis. The incidence rates of CNS metastasis from primary BC with or without ocular metastasis were 6% and 28%.<sup>[10]</sup> In this case, the brain MRI showed a small suspicious metastasis of parietal lobes. Therefore, we suggest that patients should not neglect regular brain CT or MRI in the follow-up examinations.

The treatment for patients with CM from BC includes radiotherapy, laser therapy, cryotherapy, immunotherapy, chemotherapy, endocrine therapy, photodynamic therapy, intraocular injection of anti-VEGF drugs, etc.<sup>[13]</sup> The standard treatment for CM is still radiotherapy and the rates of complete response and visual improvement are reported to be 80% and 57% to 89%, respectively.<sup>[14]</sup> Most CMs from BC were hormone receptor (HR) positive, for which endocrine therapy is effective. Manquez et al<sup>[15]</sup> used aromatase inhibitors (AIs) to treat 17 ER and PR positive patients with CM arising from BC, 10 of whom had significant positive effects, circumventing the therapy and the side effects of EBRT for the eyes. Our patient was treated with letrozole and the blurred vision in her left eye improved slightly. In recent years, much attention has been paid to targeted therapy using intraocular injection of antiangiogenic drugs. Although much of the literature reports satisfying local remission, there are many cases of failure.<sup>[16,17]</sup> In general, CM arising from BC often indicates a poor prognosis with an average survival time of 7 to 32 months.<sup>[18]</sup>

It is believed that only 2% to 5% of BC patients develop bronchial metastasis (BM).<sup>[19]</sup> The BC patient in our report was diagnosed with CM and BM, which is rare, but demonstrates that there may be a prolonged period of time from the primary tumor diagnosis to the occurrence of CM and the slow progression of malignant tumors implanted in the trachea and bronchi. The development of the BM may differ in each case, due to the different treatments of the primary tumor. Some studies have shown that almost 36% metastasis from BC will change their ER status compared with the primary sites, while 54.2% will experience a change in PR status.<sup>[20]</sup> Although the IHC results (ER and PR status) from the delayed metastases seemed to be different from the surgical pathological results 28 years ago, this may be partially explained by the changes in criteria for ER and PR status in IHC during the past 28 years.



**Figure 7.** Magnetic resonance image (MRI) showing the right parietal lobe lesion in the brain before (A) and after (B) endocrine therapy: the lesion of right parietal lobe (arrow) had disappeared. MRI=magnetic resonance image.

Most patients with CM arising from BC present with symptoms of cough, hemoptysis, chest pain, or shortness of breath, although some may be asymptomatic. In addition to the symptoms mentioned above, the patient also complained of dysphagia, which indicates the compression and invasion of the enlarged mediastinal lymph nodes to the esophagus. Chemotherapy may be the initial choice to combat the tumor burden in the chest, but was refused by the patient. Due to the positive ER and PR status, as determined by IHC, she began endocrine therapy with letrozole. The thoracic CT scan administered three months later indicated that the left lung metastatic lesions were significantly reduced. The patient's clinical symptoms improved significantly and the continuance of endocrine therapy was considered to be a wise choice.

The prognosis of patients with BM is poor in some studies. Sørensen<sup>[21]</sup> reported that BM patients survived an average of 15.2 months from the time of BM diagnosis. One study reported that the median survival time was 7 to 18 months.<sup>[22]</sup> Some patients have a longer survival time, but the underlying mechanism is still unclear. Delayed metastasis of BC to CM is very rare and could easily be ignored or misdiagnosed. There is no standard treatment for such circumstances, and individualized treatment must be taken into consideration. The prognoses of BC with CM and BM are still not optimistic and efforts to improve the patient's quality of life (QoL) should be initiated.

## 6. Conclusion

We report a rare case of late distant recurrence of HR positive breast cancer. In cases involving multiple lesions after mastectomy of HR positive breast cancer, clinicians should consider late distant recurrence and pay attention to follow-up examinations even more than 20 years after the surgery.

## Author contributions

**Conceptualization:** Xiaochuan Wang.

**Data curation:** Xiaochuan Wang.

**Project administration:** Linzhu Zhai.

**Writing – original draft:** Zhijie Luo, Qin Cai.

**Writing – review & editing:** Yuanyuan Zhao, Siying Fu, Linzhu Zhai.

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