

## Case Report

# Second primary lung cancer after a first breast cancer: a case report and critical literature review

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**Abstract:** A rare case was presented of a 56-year-old postmenopausal female with synchronous bilateral pulmonary nodules 1 year after modified radical mastectomy and radiotherapy for breast cancer. The patient was empirically misdiagnosed as recurrence of breast cancer and was given improper medication initially. Because the first cycle chemotherapy using docetaxel and pirarubicin resulted in disease progression, simultaneous biopsy of the bilateral pulmonary nodules was performed, and the pathological evidence revealed the correct diagnosis of metachronous primary pulmonary adenocarcinoma. It shows that second primary cancer of different types should be kept in mind during the differential diagnosis of newly emerged lesions in patients with a first cancer history. Herein, this special case and related literatures are presented for discussion.

**Keywords:** Second primary cancer, metachronous primary cancer, breast cancer, lung cancer

## Introduction

Synchronous and metachronous multiple primary tumors are two or more malignancies which are presented in an individual without any relationship between each other at initial diagnosis. Personalized diagnosis and management of breast cancer according to the standards of precision medicine enables improved tumor characterization and optimal therapy to minimize recurrence [1]. Patients with breast cancer history are at risk for non-small-cell lung cancer (NSCLC) [2]. It is reported that lung cancers account for 5% of second primary cancers after breast cancer [3]. Similar reports of second primary lung cancer after a first breast cancer are summarized and shown in **Table 1**, which indicates that the prevalence rate is nearly 0.84%, meanwhile, the time interval between the two cancers is 1-26 years, furthermore, radiotherapy for breast cancer is probably a risk factor of the occurrence of lung cancer.

Nevertheless, second non-breast primary malignancies after a first breast cancer could be

empirically misdiagnosed, followed by unsuitable treatment consequently. The diagnostic dilemma and challenge of tumor origin could be settled by immunohistochemistry and molecular markers, as a timely corrected therapy is of vital importance for the patients to achieve better prognosis [7].

However, misdiagnosis of multiple regular pulmonary nodules in patients after a first breast cancer is truly hard to avoid completely. In the era of precision medicine, empirical misdiagnosis should be diminished in accordance with the essential principles of personalized therapy. Herein, a special case of second primary lung cancer after a first breast cancer is presented for discussion, followed by a brief review of related literatures, with the aim to summarize the etiology and molecular features of second primary cancer for differential diagnosis and timely treatment.

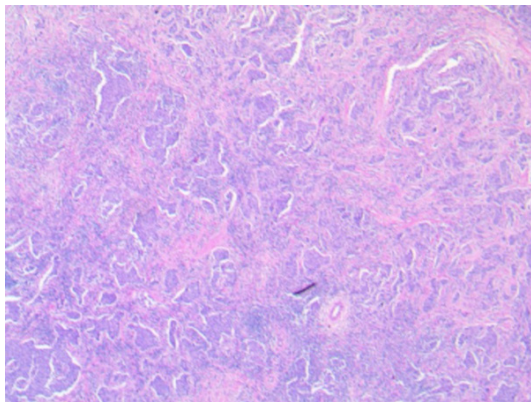
## Case presentation

An immune-competent, non-smoking and non-alcoholic, 56-year-old married and postmeno-

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**Table 1.** Reports regarding second primary lung cancer after a first breast cancer

Author	Sample	Prevalence rate	Interval between two cancers, years	Cases after radiotherapy
Milano [2]	3529	Not available	Range 5-26	1637 (46.4%)
Schonfeld [3]	1862	0.84%	Average 5.6	Not available
Grantzau [4]	151	Not available	Range 1-26, mean 12	151 (100%)
Reinmuth [5]	69	Not available	Not available	Not available
Yamato [6]	1	Not available	16	1 (100%)



**Figure 1.** Postoperative pathology indicated infiltrating ductal carcinoma of left breast 1 year ago (hematoxylin and eosin staining; magnification,  $\times 200$ ).

pausal female was admitted to our hospital for chest stuffiness, pectoralgia, palpitation as well as irritating cough for nearly 1 month and significant loss of weight during the past 6 months, without sputum, hemoptysis, fever or chills, on suspicion of recurrence and dissemination of breast carcinoma. The patient underwent modified radical mastectomy 12 months ago for breast cancer (**Figure 1**), and postoperative radiotherapy at a total dose of 50 Gy in 20 fractions, followed by tamoxifen for 12 months. Her family and social history was unremarkable, without endocrine diseases such as diabetes mellitus or hyperthyroidism, while a thorough physical examination just indicated bilateral respiratory harshness and absence of left breast. To rule out pneumonia and malignancy, serum tests were carried out subsequently. However, the laboratory examinations including fungus antigen, CD4+ lymphocyte count, human immunodeficiency virus (HIV) antibody, and serum tumor markers including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), squamous cell carcinoma (SCC), alpha fetal protein (AFP)

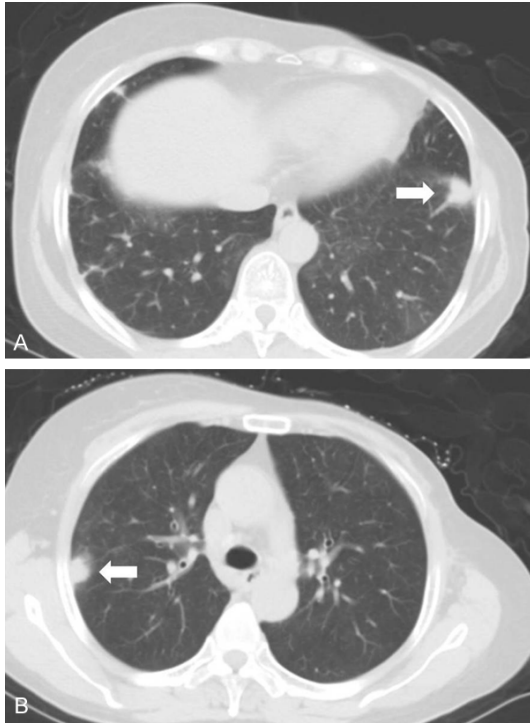
and neuron specific enolase (NSE) were all in normal range. Meanwhile, repeated fungal cultures of her sputum were negative. Besides, chest and abdomen computed tomography (CT) scan on admission revealed radiation pneumonitis, and bilateral morphologically irregular high-

density lesions with moderately enlarged mediastinal lymph nodes, mimicking the recurrence and pulmonary dissemination of breast cancer (**Figure 2**). Her bone emission computed tomography (ECT) image was normal. Although positron emission tomography-computed tomography (PET-CT) scan may be helpful for the differential diagnosis, it was not carried out because it was not covered by the health insurance of this patient.

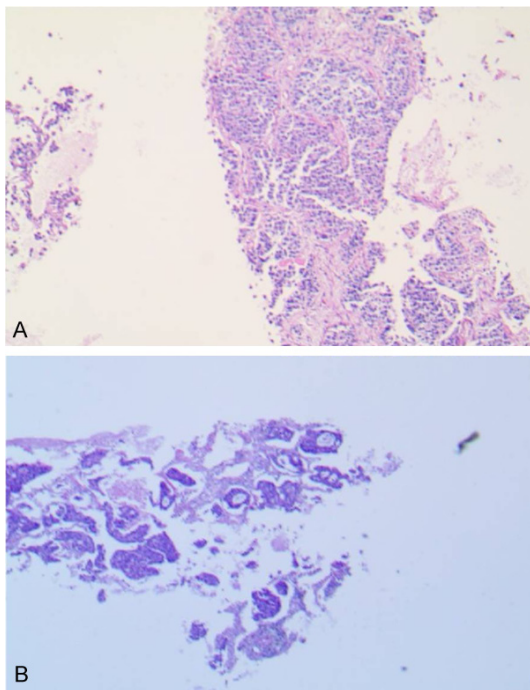
Initially, based on the above findings, the patient was misdiagnosed as end stage, recurrent breast cancer, and diagnostic biopsy of the pulmonary nodules was intentionally ignored with the aim to avoid further tumor contamination. Therefore, chemotherapy, targeted therapy and symptom-triggered psychological intervention combined with best supportive care were assumed to be the optimal therapeutic regimen after multidisciplinary consultation, which was approved by the Ethical Committee of Xuzhou Central Hospital. However, the patient was evaluated as progressive disease (PD) according to the standards of RECIST (Response Evaluation Criteria in Solid Tumors) after 1 cycle of chemotherapy using docetaxel (75 mg per square meter of body surface area) and pirarubicin (40 mg per square meter of body surface area), as the CT reexamination indicated enlarged and newly emerged pulmonary nodules.

Subsequently, a re-consultation was requested by the Ethical Committee. Bilateral CT-guided percutaneous biopsy of the pulmonary nodules located in both side, including the lesion which was adjacent to the left breast, revealed the correct diagnosis as second primary pulmonary adenocarcinoma pathologically (**Figure 3**). Besides, further immunohistochemical staining of the specimen demonstrated positive expression of cytokeratin 7, Ki-67 (10%)

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**Figure 2.** Chest CT image on admission revealed bilateral pulmonary lesions and radiation pneumonia, mimicking dissemination of breast cancer after surgery.



**Figure 3.** Both the left-sided (A) and right-sided (B) pulmonary lesions were pathologically confirmed as primary pulmonary adenocarcinoma after bilateral fine-needle aspiration biopsy (hematoxylin and eosin staining; magnification,  $\times 200$ ).

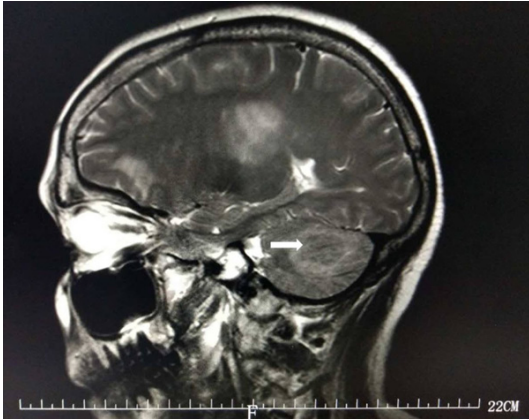
and thyroid transcription factor-1 (TTF-1), and negative expression of cytokeratin 5/6, in accordance with a clinical staging of cT4N3-M1a according to the 7<sup>th</sup> edition of American Joint Committee on Cancer staging system for lung cancer. In addition, molecular studies demonstrated epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement. However, the patient could not afford targeted therapy using monoclonal antibody for financial reasons. Accordingly, the treatment regimen was changed immediately after the corrected diagnosis.

Partial response (PR) had been achieved after the administration of 6 cycles of pemetrexed (500 mg per square meter of body surface area) plus cisplatin (75 mg per square meter of body surface area) chemotherapy with controlled moderate adverse events, followed by 2 cycles of single pemetrexed (500 mg per square meter of body surface area), meanwhile, zoledronic acid (4 mg) was added concurrently every 21 days for the patient. Then the patient maintained stable disease (SD) thereafter for 12 months. However, the enhanced cranial magnetic resonance images (MRI) of the patient revealed scattered brain metastasis after another interval of 6 months (**Figure 4**), but whole brain radiotherapy was not carried out because of her poor performance status and gradually worsening quality of life, and she lost to follow up 19 months after this admission.

### Discussion

The incidence of second primary cancers of different origin after a first malignancy is increasing, and the most common sites of the first neoplasms include breast, prostate, colorectum, skin, the head and neck, bladder and ureter, while the most common sites of the second neoplasms include breast and lung, which indicates that about 1/8 of the incidental neoplasms during the follow up after the diagnosis and therapy of the first tumor are second neoplasms [8]. Women treated for breast cancer have increased risk of second malignancies including contralateral breast cancer, sarcomas, leukaemia, lung cancer and gynaecological cancer, as compared to the general population [9]. Specifically, radiotherapy for breast cancer increases the risk of second non-breast cancer such as cancer of the lung,

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**Figure 4.** Cranial MRI revealed scattered brain metastasis during the follow up.

esophagus and sarcomas at exposed sites, with the highest risk at 15 or more years after the diagnosis of breast cancer [10, 11]. The median time from breast cancer treatment to second lung cancer diagnosis is reported to be 12 years (range from 1 to 26 years) [4]. However, a history of previous malignancy does not significantly impair outcome of the patients with second lung cancer [5].

There are several risk factors for the development of second primary cancers after a first breast cancer. Firstly, estrogen plays an important role in lung cancer carcinogenesis and progression, which adversely affects the prognosis of these patients [12]. Secondly, both the risk for a second lung cancer after a negative estrogen receptor [ER(-)] first breast cancer and the risk for a second ER(-) breast cancer after a first lung cancer is increased simultaneously [3], whereas second lung cancer rates are significantly elevated after ER(-), but not ER(+) breast cancer [3]. Thirdly, radiotherapy is proved to be associated with an excess risk of second non-breast malignancies in organs adjacent to the previous treatment fields after radiation [13]. Matrix metalloproteinases (MMPs) are related to the enhanced invasiveness and angiogenesis of cancer cells after radiation exposure, and they are directly linked with the breakage of complete extracellular matrix (ECM) and breast cancer metastases raised in bone, lung and brain tissues after radiotherapy, which might be ascribed to the ionizing radiation-induced carcinogenesis [14]. Therefore, the growing number of long-term survivors after breast cancer high-

lights an improved precise diagnosis and therapy during the life-long follow up.

Nevertheless, it is difficult to determine whether a patient with bilateral pulmonary nodules is synchronous primary tumors or tumor metastasis, and it is noteworthy that if radical resection can be performed, an aggressive surgical approach is often warranted after demonstrating no mediastinal nodal involvement [15]. Similarly, patients harboring multiple primary lung cancers have better overall survival than the patients with intrapulmonary metastasis of lung cancer [16]. Besides, the nervous system plays an important role in the regulation of epithelial homeostasis and tumorigenesis, and it is reported that perineural invasion is a potential reason of bone metastases [17]. As for the presenting patient, preventive whole-brain radiotherapy is not sustainable due to compromised performance status after the second course of chemotherapy.

On the other hand, precision medicine has an important role for breast cancer patients [18]. Noninvasive PET imaging offers complementary information including tumor burden, metabolism, receptor status and proliferation to traditional tissue biomarkers [19], which could be used to avoid overlooking of second primary cancers. Additionally, driver mutation remains the biggest challenge because no validated oncogenic drivers of breast cancer exist except ER, human epidermal growth factor receptor type 2 (HER2), phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA) and AKT1 [20]. Comprehensive genomic profiling technologies including molecular testing for EGFR, ALK, and v-Ki-ras2-Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations of bilateral pulmonary nodules are helpful to distinguish intra-pulmonary metastases from multiple synchronous primary tumors [21]. See comment in PubMed Commons below For example, it is reported that the invasive tumor sample of synchronous primary pulmonary adenocarcinomas has 27 exclusive somatic mutations, as compared with in-situ and adjacent normal tissues [22].

In summary, this presenting case demonstrates the necessity of simultaneous biopsy of different lesions in an individual patient, especially for those who have a first primary tumor history, with the aim to diminish empirical

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misdiagnosis and subsequent inappropriate treatment.

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This study was approved by the Ethics Committee of Xuzhou Central Hospital. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

### Disclosure of conflict of interest

None.

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