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CASE REPORT

Multiple primary lung cancer versus intrapulmonary metastatic cancer: A case of multiple pulmonary nodules

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Abstract

A preoperative chest computed tomography examination of the right breast in a 52-year-old woman with breast cancer revealed multiple nodules in both lungs. The nodule in the apical segment of the upper lobe of the right lung was larger, at a diameter of approximately 2.1 cm. The patient underwent resection of the right breast, followed by thoracoscopic wedge resection of four pulmonary nodules. Hematoxylin and eosin staining and immunohistochemistry showed that the nodules in the apical and anterior segments of the upper lobe and the paravertebral nodule in the lower lobe of the right lung were primary adenocarcinoma, and the subpleural nodule in the lower lobe of the right lung was infiltrated with inflammatory cells. Exon sequencing was conducted in the resected tissue samples and blood specimens. According to the characteristics of the somatic mutations, the nodule in the apical segment of the upper lobe of the right lung was primary lung adenocarcinoma, the nodule in the anterior segment of the upper lobe and the paravertebral nodule in the lower lobe of the right lung were intrapulmonary metastatic cancer, and the subpleural nodule in the lower lobe of the right lung indicated early stage tumor progression. This case provides new evidence that conducting gene detection in multiple tissue samples from patients who have undergone resection may assist to determine the relationship among multiple nodules in the lung to exclude lung metastasis of breast cancer.

Introduction

Multiple primary lung cancer (MPLC) refers to two or more primary malignant tumors occurring simultaneously or successively in the lung of the same patient, with no occurrence of N2/N3 lymph node or systemic metastasis. The distinction between MPLC and intrapulmonary metastatic cancer is of great importance to clinical treatment and prognosis. At present, clinical features, imaging, and pathological features are mainly used to comprehensively determine and distinguish MPLC and intrapulmonary metastatic cancer. However, if the pathological type and imaging features are similar, it is difficult to distinguish between the two. Recently, developments in gene mutation studies have provided a molecular basis for identifying MPLC and intrapulmonary metastatic cancer.

Case presentation

A 52-year-old Han Chinese woman was admitted to the Department of Thoracic Surgery of Beijing Friendship Hospital on 20 November 2017 after multiple nodules were detected in the right lung. The patient had a five-year history of hypertension, denied any history of smoking and drinking, and had a family history of lung disease. On 2 November 2017, she had undergone reserved mastectomy for right breast cancer followed by axillary lymph node dissection at the Department of General Surgery of Beijing Friendship Hospital. Postoperative pathology showed infiltrating ductal carcinoma in the right breast and metastases in 1–20 right axillary lymph nodes. The chest computed tomography (CT) examination showed multiple nodules in both lungs; metastasis was not excluded. The nodule in the apical segment of the upper

lobe of the right lung was larger but was not confirmed as malignant. Whole-body positron emission tomography (PET)-CT examination further showed that the nodule in the apical segment of the upper lobe of the right lung was larger; the lesion was considered to be malignant, thus indicating a strong possibility of peripheral lung cancer. No abnormal increase in F^{18} fluorodeoxyglucose (FDG) metabolism was found in the other pulmonary nodules and mediastinal and hilar lymph nodes. Follow-up observation was recommended. It was difficult to preoperatively diagnose whether the multiple nodules of both lungs were primary lung cancer with intrapulmonary metastasis, or lung metastasis of breast cancer. The following two surgical programs were recommended after general discussion among the whole department:

Program 1: Video-assisted thoracoscopic wedge resection of the nodule in the upper lobe of the right lung and wedge-shaped resection of the nodule in the lower lobe of the right lung, followed by resection of the nodule in the upper lobe of the right lung and lymph node dissection, depending on the results of the intraoperative frozen section.

Program 2: Thoracoscopic excision of the nodule in the upper lobe of the right lung, mediastinal lymph node dissection, and dynamic observation of the remaining nodules.

Preoperative CT-guided microcoil localization was conducted on the small nodules of the upper lobe of the right lung, and Program 1 was implemented on 24 November 2017. A total of four nodules were resected during the surgery: (i) a nodule in the apical segment of the upper lobe of the right lung, measuring $2.1 \times 1.2 \times 1.1$ cm^3; (ii) a nodule in the anterior segment of the upper lobe of the right lung approximately 0.4 cm in diameter; (iii) a subpleural nodule in the lower lobe of the right lung approximately 0.4 cm in diameter; and (iv) a paravertebral nodule in the lower lobe of the right lung approximately 0.6 cm in diameter (Fig 1). Postoperative pathology showed that the nodules in the apical and anterior segments of the upper lobe of the right lung and the paravertebral nodule in the lower lobe of the right lung were all primary lung adenocarcinoma. The subpleural nodule in the lower lobe of the right lung was infiltrated with inflammatory cells. The choice of surgical procedure was reasonable based on the postoperative pathological results.

Hematoxylin and eosin (HE) staining and immunohistochemistry were performed. HE staining of the three surgically resected pulmonary nodules showed adenocarcinoma infiltration in the lung tissue, and acinar was the dominant type (Fig 2a,b,d). The results of immunohistochemical detection showed aspartic proteinase A (Napsin A) (+), cytokeratin (CK) 7 (+), and thyroid transcription factor 1 (TTF-1)(+). The positive Ki-67 rate in the nodules of the apical segment of the upper lobe of the right lung (20%), the anterior segment of the upper lobe of the right lung (15%), and the paravertebral nodule in the lower lobe of the right lung (15%) indicated primary lung adenocarcinoma (Table 1). HE staining of the breast cancer specimen showed a glandular tubular structure and the lesion was ductal carcinoma in situ (Fig 2e,f). The results of immunohistochemical detection showed that estrogen receptor (ER) was approximately 80% strong (+), progesterone receptor (PR) approximately 30% strong (−) medium (+), Ki-67 approximately 25% (+), E-cadherin (+), CK8 (+), and CerbB-2 (1+), which indicated breast infiltrating ductal carcinoma (Table 1). HE staining of the pulmonary inflammatory nodules showed benign micronodular hyperplasia in the stromal spindle cells (Fig 2c), and immunohistochemistry showed CK7 alveolar epithelium (+), CD31 blood vessel (+), Syn (−), CgA (−), and actin (−).

Exon sequencing was conducted in the resected tissue samples and blood specimens, and the relationships among their somatic mutations were compared. Both *TP53* and *EGFR* gene mutations were found in all three surgically resected pulmonary nodules, and their base alterations, amino acid alterations, and functional areas were the same. Although *TP53* gene mutation existed in both the breast cancer lesion and the nodule in the upper lobe of the right lung, their base alterations, amino acid alterations, and functional areas were different. The frequencies of *TP53* and *EGFR* mutations in the apical segment of the upper lobe of the right lung were 39.3% and 20%, respectively, which were significantly higher than in the other two nodules. Moreover, rare nucleophosmin (*NPM1*) mutation existed in both the subpleural nodule in the lower lobe of the right lung and the paravertebral nodule in the lower lobe of the right lung. On the first day after surgery, blood samples were collected for gene detection (Table 2).

Discussion

The probability of detecting pulmonary nodules by chest CT examination is high, as pulmonary multiple nodules are common and most are benign. The results of the National Lung Screening Trial in the United States showed that the probability of detecting a pulmonary nodule in a high-risk population via chest CT screening was as high as 27.3%.[1] The 2013 Fleischner Society guidelines recommend that for multiple ground-glass nodules with prominent lesions, the major lesions need to be further treated. If CT examination confirms the presence of the lesion three months after the first examination, further diagnosis and treatment are suggested for larger lesions, especially for lesions with an internal solid component diameter of > 5 mm.[2] A large number of clinical studies have reported the existence of several benign nodules around malignant

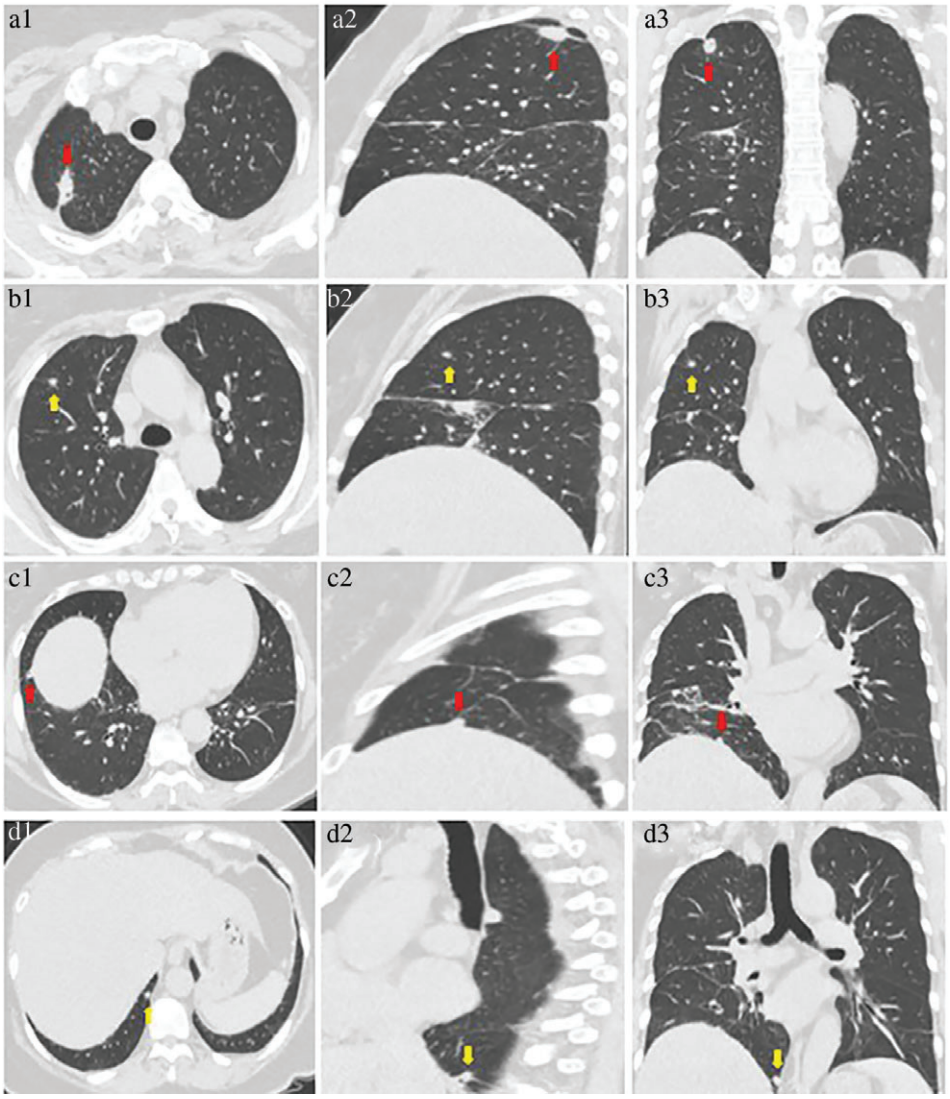

Figure 1 Three-dimensional computed tomography image reconstruction of (**a1–3**) the 2.1 cm diameter nodule in the apical segment and the (**b1–3**) the 0.4 cm diameter nodule in the anterior segment of the upper lobe of the right lung; (**c1–3**) the 0.4 cm diameter subpleural nodule, and (**d1–3**) the 0.6 cm diameter paravertebral nodule in the lower lobe of the right lung.

nodules; the diameter of these small nodules is usually < 4 mm, indicating a low probability of malignancy.[3] In this study, the patient had a history of right breast cancer, and whole-body PET-CT examination revealed a malignant larger nodule in the apical segment of the upper lobe of the right lung; no abnormal increase was found in FDG metabolism in the other pulmonary nodules or mediastinal and hilar lymph nodes. Follow-up observation was recommended. The nodule in the upper lobe of the right lung was diagnosed as primary lung cancer in another hospital, and pulmonary lobectomy was suggested. The other nodules were considered benign lesions and continuous observation was suggested. However, this therapeutic regimen would have led to postoperative pathological staging and the incorrect therapeutic regimen. Therefore, several therapeutic regimens based on the patient's history and clinical characteristics were developed. The diagnosis of breast cancer was definite, but the possible relationships among the multiple nodules in the lung were as follows: (i) if all of the lesions were lung metastasis of breast cancer, surgery would produce no benefit; (ii) if the node in the apical segment of the upper lobe of the right lung was malignant and the other lesions were benign, pulmonary lobectomy along with mediastinal lymph node dissection was feasible; (iii) if the node in the apical segment of the upper lobe of the right lung was considered a malignant lesion and the remaining lesions were pulmonary metastases, surgery would produce no benefit; and (iv) if all of the pulmonary nodules were MPLC, lobectomy of the upper lobe of the right lung, mediastinal lymph node dissection, and wedge resection of the lower lobe of the right lung was feasible.

With the rapid development and application of molecular diagnostic technologies, understanding of non-small-cell lung cancer (NSCLC) has increased from the tissue

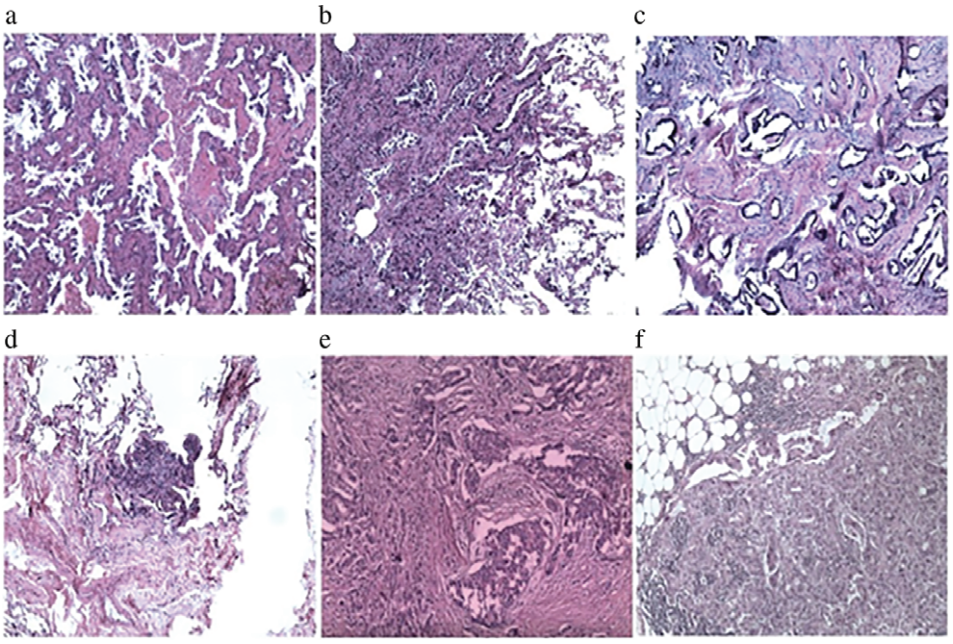

Figure 2 Hematoxylin and eosin (HE) staining of the nodule (**a**) in the apical segment and (**b**) the anterior segment of the upper lobe of the right lung. Adenocarcinoma infiltration was observed in the lung tissue, and acinar was the dominant type. (**c**) HE staining of the subpleural nodule slice in the lower lobe of the right lung. Inflammatory cell infiltration was observed in the lung tissue. (**d**) HE staining of the paravertebral nodule slice in the lower lobe of the right lung. Adenocarcinoma infiltration was observed in the lung tissue, and acinar was the dominant type. (**e**) HE staining of the lump slice in the right breast, with the breast infiltrating ductal carcinoma. The lesion was ductal carcinoma in situ. (**f**) HE staining of the lymph node slice in the right armpit.

level to the molecular level, and more tumor-driven genes have successively been found. *EGFR* gene mutation is the most common mutation type in an Asian population with NSCLC.[4] *EGFR* mutation in patients with NSCLC mainly occurs in the first four exons of the tyrosine kinase (TK) region (18–21). At present, more than 30 mutations have been found in the TK region, and the most common mutations occur in exons 19 and 21, at a rate of approximately 85%.[5,6] The probability of *EGFR* gene mutation in patients with NSCLC ranges from 30% to 60%, and *EGFR* gene mutation between primary and metastatic lesions is consistent.[7,8] *TP53* gene mutation is also significant to the occurrence and development of NSCLC and the probability of mutation is approximately 40–60%, regardless of whether an *EGFR* mutation occurs.[9] A study showed that the *TP53* mutation rates in patients with NSCLC in the primary lung tumor and metastatic lymph nodes were 23.2% and 21.4%, respectively. The *TP53* gene mutation had 92.9% correlation in the primary lung tumor and metastatic lymph nodes, and the *TP53* gene mutation preceded lymph node metastasis and continued to play a role in tumor development.[10]

In our patient, both *EGFR* and *TP53* gene mutations were found in the three malignant pulmonary nodules resected. Their base alterations, amino acid alterations, and functional areas were all the same, indicating that the cells showed the same clonality based on specific gene mutations. Although *TP53* gene mutation occurred in both the breast cancer lesion and the nodule in the apical segment of the upper lobe of the right lung, the base alterations, amino acid alterations, and functional areas were different. The mutant genes in the breast cancer lesion were more significant than those in the nodule in the apical segment of the upper lobe of the right lung, indicating that the cells showed the same clonality based on specific gene mutations. The allele frequency of gene mutation could reflect the time sequence of mutant genes; the greater the allele frequency of individual somatic mutation, the earlier the mutation occurred.[11] The *TP53* and *EGFR* gene mutation frequencies in the nodule in the apical segment of the right upper lobe of the lung were 39.3% and 20%, respectively, which were significantly higher than in the other two nodules, indicating that the nodule in the apical segment of the upper lobe of the right lung occurred first. To sum up, the nodule in the apical segment of the upper lobe of the right lung was considered primary lung adenocarcinoma and the nodules in the anterior segment of the upper lobe and the paravertebral nodules in the lower lobe of the right lung were considered intrapulmonary metastatic cancer. In addition, *NPM1* mutation occurred in the subpleural and paravertebral nodules in the lower lobe of the right lung. *NPMI* gene mutation is a molecular genetic anomaly with the highest detection rate in adult acute myeloid leukemia. *NPMI* can regulate the activities of the tumor suppressor genes *p14* and *p53* and participate in cell proliferation.[12–14] However, *NPMI* gene mutation is not common in patients with NSCLC, suggesting that the subpleural nodules in the lower lobe of the right lung in this patient might indicate early stage tumor progression.

The latest tumor node metastasis (TNM) classification system proposes tailoring the TNM classification of multiple pulmonary sites of lung cancer to reflect the unique

Table 1 Comparison of immunohistochemistry results

Immunohistochemistry /Lesion	Nodule in the apical segment of the upper lobe of the right lung	Nodule in the anterior segment of the upper lobe of the right lung	Subpleural nodule in the lower lobe of the right lung	Paravertebral nodule in the lower lobe of the right lung	Breast lesion
CK20	(–)	None	None	None	None
CK7	(+)	(+)	Alveolar epithelium (+)	(+)	None
TTF-1	(+)	(+)	None	(+)	None
Napsin A	(+)	(+)	None	(+)	None
CK5/6	(–)	(–)	None	(–)	Glandular epithelium (–)
P63	Part(+)	(–)	None	(–)	(–)
Calponin	(–)	(–)	None	(–)	(–)
ER	(–)	(–)	None	(–)	Approximately 80% strong+
PR	(–)	(–)	None	(–)	Approximately 30% strong–medium +
CerbB-2	(1+/2+)	Approximately 1+	None	Approximately 1+	1+
Ki-67	20% (+)	Approximately 15%	Approximately 2 (+)	Approximately 15%	Approximately 25% (+)
E-Cadherin	Membrane (+)	(+)	None	(+)	(+)
P120	Membrane (+)	(+)	None	(+)	Membrane (+)
CK8	(+)	(+)	None	(+)	(+)
MLH1	(+)	None	None	None	None
MSH2	(+)	None	None	None	None
MSH6	(+)	None	None	None	None
PMS2	(+)	None	None	None	None
P40	None	(–)	None	(–)	None
Syn	None	None	(–)	None	None
CgA	None	None	(–)	None	None
CD31	None	None	Blood vessel (+)	None	None
Actin	None	None	(–)	None	None
Vimentin	None	None	Focal cell (+)	None	None
HMB45	None	None	(–)	None	None
GFAP	None	None	(–)	None	None

Immunohistochemical detection was conducted in the nodules of the apical and anterior segments of the upper lobe of the right lung and subpleural and paravertebral nodules of the lower lobe of the right lung, and their relationships were compared. CgA, chromogranin A; CK, cytokeratin 20; E-cadherin, epithelial cadherin; ER, estrogen receptor; Napsin A, aspartic proteinase A; PR, progesterone receptor; Syn, synapses; TTF-1, thyroid transcription factor-1.

aspects of the four different patterns of presentation. Separate tumor nodule(s) (of the same histologic type) are classified on the basis of nodule location relative to the primary tumor site. Multifocal GG/L adenocarcinoma should be classified by the T category of the lesion with the highest T, along with the number of lesions (#) or simply (m) for multiple indicated in parentheses, and an N and M category that applies to all of the multiple tumor foci collectively.[15] In a study cohort of clinical stage T4NXM0 patients, postoperative patients refused chemotherapy and chose oral TKI (gefitinib) treatment. After six months, complications of mild pulmonary fibrosis occurred and treatment was discontinued; however, the general condition of the patients was good, no signs of recurrence were found, and long-term prognosis was pending further follow-up. In patients with frequently occurring lung nodules, if pathological results cannot differentiate multiple primary lung cancer and intrapulmonary metastatic cancer, excision of the lesion would allow testing for *TP53* and *EGFR* mutation. Changes in base alterations, amino acid alterations, and functional areas can indicate whether the lesions show the same clonality. Based on the order speculated by the frequency of allelic gene mutation, a judgment between primary tumor and metastasis could then be made. In our case, PET-CT examination revealed a larger malignant nodule in the apical segment of the upper lobe of the right lung but no abnormal increase in FDG metabolism in the other pulmonary nodules or mediastinal and hilar lymph nodes. However, pathologic results revealed three malignant nodules. The reason for this discrepancy in results may be because pathological features significantly influence FDG uptake in solid-type pulmonary adenocarcinomas. In particular, the fact that colloid/mucinous/lepidic adenocarcinomas have a significant tendency to generate false-negative PET findings warrants attention.[16]

In conclusion, distinguishing two different pulmonary nodules, that is, primary lung cancer and intrapulmonary metastasis from MPLC in clinical practice is quite

Table 2 Comparison of gene detection results

Lesion/Gene	Mutant gene	Base alternation	Amino acid alternation	Functional area	Mutation frequency (%)	Pathological result
Nodule in the apical segment of the upper lobe of the right lung	TP53	c.544delT	p.C182Afs*65	EX5	39.3	Primary adenocarcinoma of the lung
	EGFR	c.2573T > G	p.L858R	EX21	20.0	
Nodule in the anterior segment of the upper lobe of the right lung	TP53	c.544delT	p.C182Afs*65	EX5	8.7	Primary adenocarcinoma of the lung
	EGFR	c.2573T > G	p.L858R	EX21	3.3	
Paravertebral nodule in the lower lobe of the right lung	TP53	c.544delT	p.C182Afs*65	EX5	2.0	Primary adenocarcinoma of the lung
	EGFR	c.2573T > G	p.L858R	EX21	1.9	
	NPM1	c.523GAT[6 > 5]	p.D175[6 > 5]	EX7	1.7	
Subpleural nodule in the lower lobe of the right lung	NPM1	c.523GAT[6 > 5]	p.D175[6 > 5]	EX7	1.8	Inflammatory cell infiltration
Breast lesion	TP53	c.743G > A	p.R248Q	EX7	33.1	Infiltrating ductal carcinoma
	PTEN	c.1027-2A > G	—	IVS8	31.3	
	C11orf30	c.3844G > C	p.E1282Q	EX21	14.3	
	GATA3	c.922-3_922-2delCA	—	IVS4	8.8	
	GRIN2A	c.1124T > C	p.V375A	EX5	4.6	
	FGFR1	c.1549G > A	p.E517K	EX12	3.3	
	BRD2	c.478G > T	p.D160Y	EX4	2.4	
	TOP1	c.1149C > G	p.I383M	EX12	1.7	
	NOTCH4	c.689G > A	p.R230H	EX4	1.3	
	CUL3	c.610G > T	p.D204Y	EX5	1.1	
	TSC2	c.1073G > A	p.W358*	EX11	1.0	
	KDM6A	c.1910C > G	p.S637C	EX16	1.0	
Blood specimen	H3F3C	c.312G > C	p.L104F	EX1	1.5	—
	FH	c.817G > A	p.A273T	EX6	1.0	

Exon sequencing was conducted in the nodules in the apical and anterior segments of the upper lobe of the right lung and subpleural and paravertebral nodules in the lower lobe of the right lung, blood specimen, and breast lesion. The relationships among mutant genes, base alteration, amino acid alteration, functional area, and mutation frequency were compared.

difficult. These two different diagnoses significantly affect the treatment and prognosis of patients. Pathology is still the gold standard for the diagnosis of lung cancer; however, the staging and classification of lung cancer are challenging. In this study, determining the homology and pluralism by conducting gene detection of tissue samples and analysis of the characteristics of their somatic mutations was effective and accurate. For patients with multiple pulmonary nodules, complete resection of all ipsilateral lesions is recommended during surgery if possible. Gene detection should be conducted in all resected tissue samples, and the staging and tumor origin need to be clearly defined.

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Disclosure

No authors report any conflict of interest.

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