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CASE REPORT

Synchronous triple primary lung cancer with three different histological subtypes in the same lobe: A case report

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Lung cancer; molecular biology; multiple primary neoplasms; mutation; synchronous neoplasms.

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Abstract

Although the number of patients diagnosed with synchronous multiple primary lung cancer is growing because of increased screening and improved imaging technology, synchronous triple primary lung cancer with different histological tumor subtypes occurring in the same lobe of the lung is extremely rare. In this report, we encountered a 64-year-old male patient with three different types of nodule in the right lower lobe of the lung found on chest computed tomography (CT) scan. We believed that the patient had triple primary lung cancer, and subsequently performed a right lower lobectomy using video-assisted thoracoscopic surgery (VATS). The pathological diagnosis was the same as the presurgical diagnosis, but all the nodules were different histological subtypes. To the best of our knowledge, this is the first case reported in the literature of synchronous triple primary lung cancer with three different histological subtypes in the same lobe of the lung.

Key points

Significant findings of the study: This is the first case of synchronous triple primary lung cancer with three different histological subtypes in each tumor in the same lobe of the lung.
What this study adds: We report the details of the case with immunohistochemical and gene mutation findings, and a literature review of synchronous primary lung cancer.

Introduction

The number of patients diagnosed with synchronous multiple primary lung cancer is growing because of increased screening and improved imaging technology.[1] Synchronous triple primary lung cancer with different histological tumor subtypes occurring in the same lobe of the lung is extremely rare.[2] Here, we report such a case with the immunohistochemical findings and a literature review. It is hoped that by sharing this case that knowledge of synchronous primary lung cancer will be enhanced.

Case report

A 64-year-old male former smoker (Brinkman index: ~880) was seen complaining of chest discomfort. He had a history of combined pulmonary fibrosis and emphysema (CPFE). He did not have a previous history of carcinoma or any other comorbidity. Chest computed tomography (CT) revealed three abnormal nodules in the right lower lung lobe: 25 mm nodule, right superior segment; 20 mm nodule, right lateral basal segment; and 18 mm solid nodule, posterior basal segment (Fig 1a–c, respectively). Chest CT scan revealed interstitial changes in the bilateral dorsal

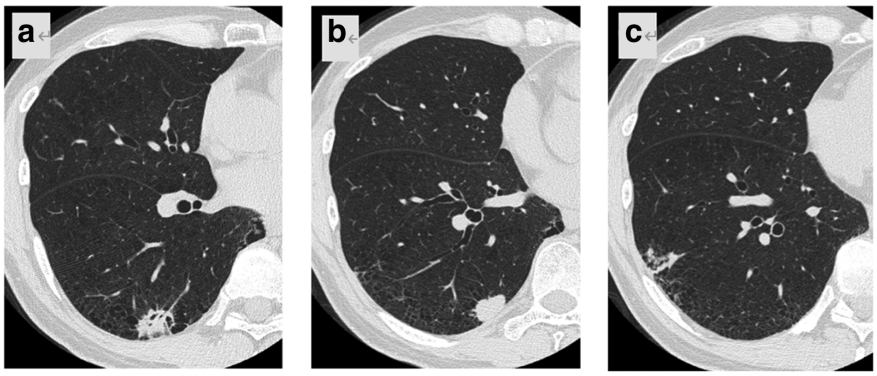

Figure 1 Chest computed tomography (CT) showing three nodules in the right lower lobe. (**a**) An irregular nodule of 25 mm in size with cavities and spiculation in the superior segment. (**b**) A solid well-defined nodule of 18 mm in size close to pleura in the posterior basal segment. (**c**) An irregular nodule which appeared to be an inflammatory change of 20 mm in size in the lateral basal segment.

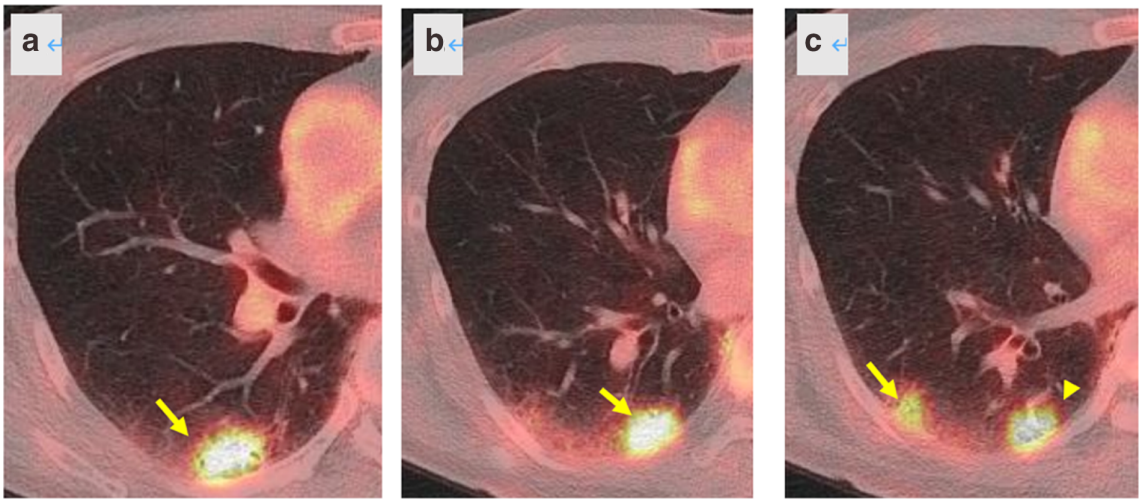

Figure 2 Positron emission tomography (PET) showing significant uptake in each nodule (arrows in each figure), with a standardized uptake value (SUV) of (**a**) 9.9 in the superior segment nodule; (**b**) 14.6 in the posterior basal segment nodule; and (**c**) 3.7 in the lateral basal segment nodule. The arrowhead indicates the tumor in (**b**) (posterior basal segment nodule).

lower lobes, suggestive of interstitial pneumonia. Positron emission tomography (PET) scan showed significant uptake in each nodule, with the following standardized uptake values: superior segment nodule: 9.9; lateral basal segment nodule: 3.7; and posterior basal segment nodule: 14.6 (Fig 2a–c, respectively). No lymph node metastasis or distant metastasis was seen. Transbronchial lung biopsy of the superior segment nodule identified squamous cell carcinoma (SCC). We diagnosed synchronous triple primary lung cancer (cT1cN0M0, c stage IA3 according to the eighth TNM classification of the Union for International Cancer Control) because the nodules were distant from each other on radiographic examination, and each had different morphological features. We performed video-assisted thoracoscopic surgery (VATS) right lower lobe lobectomy and ipsilateral mediastinal–hilar lymphadenectomy (ND2a-1). The patient's postoperative course was uneventful. Pathological findings revealed keratinizing SCC in the right superior segment (pT1aN0M0, p stage IA1), solid predominant adenocarcinoma (ADC) in the lateral basal segment (pT1bN0M0, p stage IA2), and small-cell lung cancer (SCLC) in the posterior basal segment (pT2a (pl1) N0M0, p stage IB) (Fig 3b–d, respectively). The pathological diagnosis was synchronous triple primary lung cancer with three different histological subtypes. Immunohistochemical testing was performed on the three tumors and *p53* gene hot spot mutation (exons 4–9) status evaluation (Table 1). The patient underwent adjuvant chemotherapy (cisplatin and etoposide) according to the SCLC regimen. He is alive without signs of recurrence (1 year).

Discussion

We found only one other report of synchronous triple primary lung cancer in the same lobe of the lung in the English literature.[2] The authors reported three different

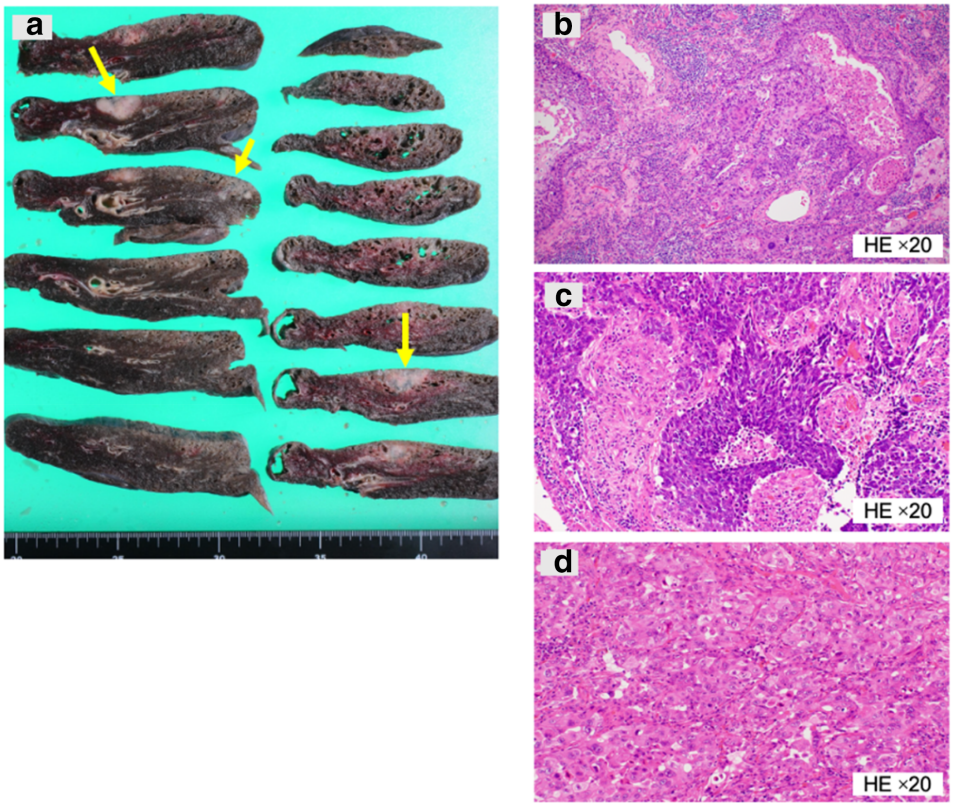

Figure 3 (**a**) Macroscopic findings showing the three white nodules in the right lower lobe. All nodules were completely separate from each other. Microscopic findings showing that each tumor had the typical features of its respective histological subtype with hematoxylin and eosin staining. (**b**) Keratinizing squamous cell carcinoma in the superior segment. (**c**) Small-cell lung cancer in the posterior basal segment. (**d**) Solid predominant adenocarcinoma in the lateral basal segment.

Table 1 Pathological features of each nodule

	TTF1	p40	Chromogranin A	Synaptophysin	CD56 (NCAM)	Neuroendocrine malformation	p53 stain	*p53* mutation
SCC (S6)	–	+	–	–	–	–	+	Unknown
SCLC (S10)	±	–	–	–	+	+	+	+ (Exon 5)
ADC (S9)	+	–	–	–	–	–	+	Unknown

ADC, adenocarcinoma; CD56, natural killer cell antigen CD56; NCAM, neural cell adhesion molecule; p40, interleukin-12 disulfide-bonded subunit p40; p53, p53 tumor suppressor gene; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; TTF1, thyroid transcription factor-1.

subtypes; however, two of the three tumors may have been combined SCLC (C-SCLC), which is defined as SCLC with additional components consisting of any of the histological types of non-small cell lung carcinoma (NSCLC).[3] The incidence of C-SCLC has been reported to range from 5% to 28%, with a higher diagnostic frequency in surgically-resected specimens.[4] In the only similar report to our case, the possibility of C-SCLC was not discussed, but the presurgical diagnosis was double primary lung cancer because the imaging findings indicated only two tumors (two lesions appeared as a single mass). We considered that the case may have been C-SCLC. In contrast, all tumors in our case were completely independent macroscopically and pathologically (Fig 3a). Each tumor also showed the typical pathological features of its histological subtype; therefore, ours is probably the first report of synchronous triple primary lung cancer with three different histological subtypes in a single lobe of the lung.

Immunohistochemical analysis showed that TTF1 was positive in ADC and slightly positive in SCLC but negative in SCC. CD56 was positive only in the SCLC; neuroendocrine features were also seen only in the SCLC. p40 was positive in the SCC tumors but negative in the other tumors. These findings are typical features of each histological subtype indicating that the histological subtypes were independent.

TP53 staining was positive in all tumors, but hot spot (exons 4–9) *p53* gene mutation was detected only in the SCLC (exon 5: c.422G > A (p.Cys141Tyr), which has been previously reported in lung ADC and SCC.[5,6] In our case, the details of the *p53* mutation status in the other two tumors remains unclear because we did not analyze

uncommon *p53* mutations. However, we suggest that the mutation in the ADC and SCC tumors might not have been the *p53* wild-type because *TP53* nuclear staining in these tumors was clearly positive. The *p53* gene plays an important role in the tumorigenesis of lung epithelial cells.[7] Our results indicate that at least the SCLC and possibly all tumors had different clonal origins. Germinal mutations and/or single nucleotide polymorphism may have elucidated a common mechanism of carcinogenesis; however, we did not perform these evaluations.

A previous report has demonstrated that heavy smoking history (especially Brinkman index >1000) is a risk factor for multiple lung ADC.[8] Our patient was a former smoker with a Brinkman index of 880, which represents a relatively light smoking history; however, smoking may have been a risk factor for the multiple lung cancer in our patient. Interstitial pneumonia is also a reported risk factor for lung cancer;[9] however, the causal relationship is unknown because the interstitial changes in our patient were relatively mild.

We are of the opinion that our case of synchronous triple primary lung cancer in the same lung lobe, with different histological subtypes, is extremely rare in surgically resected typical primary lung cancer.

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Disclosure

The authors have no conflicts of interest to declare.

References

1 Kashif M, Ayyadurai P, Thanha L, Khaja M. Triple synchronous primary lung cancer: A case report and review of the literature. *J Med Case Reports* 2017; **11**: 245.
2 Wcisło S, Misiak P, Brocki M. A case of three synchronous primary lung cancers within the same lung lobe. *Kardiochir Torakochirurgia Pol* 2016; **13**: 154–6.
3 Travis WD. The 2015 WHO classification of lung tumors. *Pathologe* 2014; **35** (Suppl 2)): 188.
4 Qin J, Lu H. Combined small-cell lung carcinoma. *Onco Targets Ther* 2018; **11**: 3505–11.
5 Vega FJ, Iniesta P, Caldes T *et al. p53* exon 5 mutations as a prognostic indicator of shortened survival in non-small-cell lung cancer. *Br J Cancer* 1997; **76**: 44–51.
6 Chang MT, Asthana S, Gao SP *et al.* Identifying recurrent mutations in cancer reveals widespread lineage diversity and mutational specificity. *Nat Biotechnol* 2016; **34**: 155–63.
7 Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. *J Biomed Biotechnol* 2011; **2011**: 583929. https://doi.org/10.1155/2011/583929.
8 Liu XD, Qu Y, Lu SS. Synchronous double primary lung cancer: A report of three cases. *Chin J Cancer Res* 2014; **26**: E17–21.
9 Tzouvelekis A, Gomatou G, Bouros E, Trigidou R, Tzilas V, Bouros D. Common pathogenic mechanisms between idiopathic pulmonary fibrosis and lung cancer. *Chest* 2019; **156**: 383–91.

