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CASE REPORT

Differential diagnosis and cancer staging of a unique case with multiple nodules in the lung – lung adenocarcinoma, metastasis of colon adenocarcinoma, and colon adenocarcinoma metastasizing to lung adenocarcinoma

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Lung; metastatic adenocarcinoma; primary adenocarcinoma; tumor-to-tumor metastasis.

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Abstract

Lung cancer is the most common cancer in the world. Despite this, there have been few cases of simultaneous primary and metastatic cancers in the lung reported, let alone coexisting with tumor-to-tumor metastasis. Herein, we describe an extremely unusual case. A 61-year-old man with a history of colon adenocarcinoma was revealed as having three nodules in the lung 11 months after colectomy. The nodule in the left upper lobe was primary lung adenocarcinoma, the larger one in the right upper lobe was a metastasis of colon adenocarcinoma, and the smaller one in the right upper lobe was colon adenocarcinoma metastasizing to lung adenocarcinoma. Our paper focused on the differential diagnosis and cancer staging of this unique case, and discussed the uncommon phenomenon of the lung acting as a recipient in tumor-to-tumor metastasis.

Introduction

It is well known that lung cancer is the most common cancer in the world and the lung receives the most metastatic tumors of any organ.[1] Despite this, there have been few cases with simultaneous primary and metastatic carcinoma in the lung reported, let alone coexisting with tumor-to-tumor metastasis.[2–6]

Herein, we describe an unusual patient who developed primary lung adenocarcinoma, metastasis of colon adenocarcinoma, and colon adenocarcinoma metastasizing to lung adenocarcinoma, simultaneously. The differential diagnosis and T staging of this unique case are discussed as follows based on the recommendations of the newly proposed international multidisciplinary classification of lung adenocarcinoma and American Joint Committee on Cancer Staging Manual (AJCC, 7th Edition).[7,8] The uncommon phenomenon of the lung acting as a recipient in tumor-to-tumor metastasis is also discussed.

Case report

Clinical findings

A 61-year-old man underwent a curative colectomy for colon adenocarcinoma on 12 October 2007. Three cycles of adjuvant chemotherapy were performed after the operation, with annual follow-up exams. On 20 September 2011, axial CT scans revealed multiple nodules in the lung, one in the apical-posterior segment of the left upper lobe with local pleural adhesion, and the other two in the right upper lobe with the smaller one extensively contacting the parietal pleura and the larger one having a pleural tag (Fig 1).

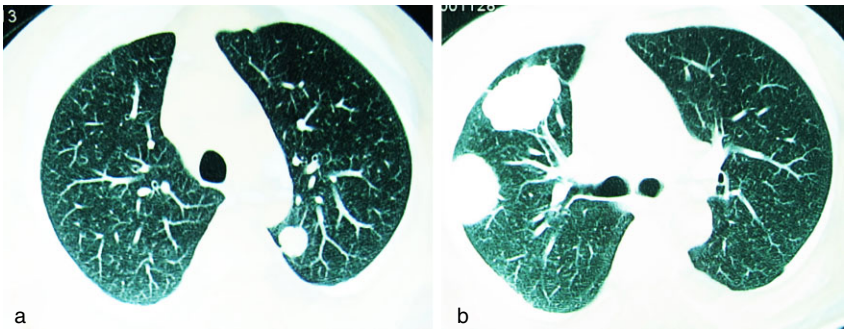

Figure 1 Axial computed tomography scans at two different levels. (**a**) A well-defined solid nodule in the apical-posterior segment of the left upper lobe with local pleural adhesion. (**b**) Two lobulated masses in the right upper lobe. The smaller one extensively contacted with parietal pleura and the larger one had a pleural tag.

Wedge resection of the left upper lobe and lumpectomy of the right upper lobe were performed on 8 October 2011. The patient was still alive on the day of follow-up, 1 January 2013.

Pathology findings

A peripheral tumor, 2.5 cm in diameter, was noted underlying pleural puckering in the left upper lobe. Microscopically, the tumor consisted of mucinous (30%) and non-mucinous cells (70%). Mucinous cells grew in an acinar pattern and non-mucinous cells in a papillary pattern (Fig 2). Mucinous cells showed cytokeratin (CK)7 positive diffusely, and CK20 and thyroid transcription factor 1 (TTF-1) positive focally. Non-mucinous cells showed CK7 and TTF-1 positive diffusely, and CK20 negative completely. Both mucinous and non-mucinous cells were CDX-2 negative (Fig 3). Elastin staining did not identify the visceral pleura invasion.

Two peripheral tumors, 5.5 cm and 3.5 cm in diameter separately, were noted in the right upper lobe, both of which attached to the pleura. The larger one was homogeneous, consisting of glandular structure lined by tall-columnar cells with nuclear pseudostratification (Fig 2) and showing the phenotype of $CK20^{+}$/$CDX\text{-}2^{+}$/$CK7^{-}$/$TTF\text{-}1^{-}$ (Fig 3). The smaller one was heterogeneous: one third of it possessed the same morphology and phenotype as the larger one, two thirds of it consisted of lepidic/papillary structure lined by non-mucinous cells (Fig 2) and showed phenotypes of $CK7^{+}$/$TTF\text{-}1^{+}$/$CDX\text{-}2^{-}$/$CK20^{-}$ (Fig 3). Elastin staining identified the visceral pleura invasion.

Lymph-vascular invasion and lymph node metastasis were not identified.

The final diagnosis was: (i) lung adenocarcinoma, mixed mucinous and non-mucinous, in the left upper lobe; (ii) metastasis of colon adenocarcinoma in the right upper lobe (the larger one); and (iii) colon adenocarcinoma metastasizing to lung adenocarcinoma in the right upper lobe (the smaller one).

Furthermore, epidermal growth factor receptor (EGFR) gene mutations were detected by immunohistochemistry (IHC) using mutation-specific antibodies (EGF Receptor [E746-A750 del Specific] [6B6] X Rabbit mAb and EGF Receptor [L858R Mutant Specific][43B2] Rabbit mAb, Cell

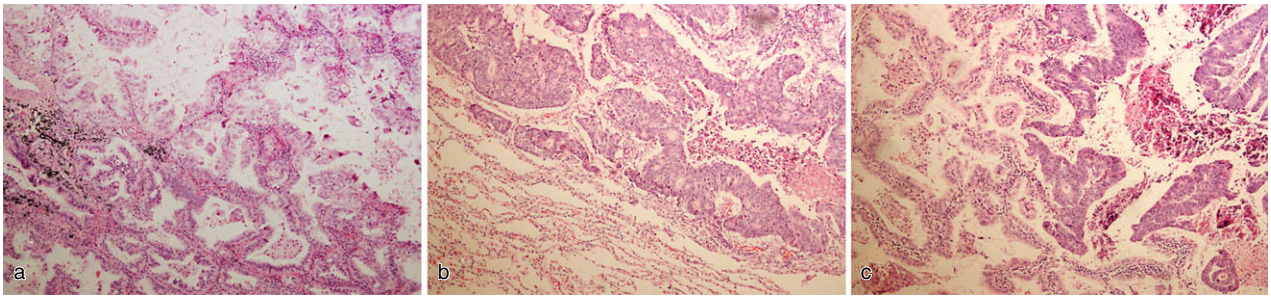

Figure 2 Histology of the three tumors (hematoxylin & eosin, original magnification ×100): (**a**) Nodule in the left upper lobe. Mucinous cells grew in an acinar pattern (up) and non-mucinous cells grew in a papillary pattern (down). (**b**) The larger nodule in the right upper lobe. The tumor was homogeneous with glandular structures lined by tall-columnar cells with nuclear pseudostratification. (**c**) The smaller nodule in the right upper lobe. The tumor was composed of two components: glandular structure lined by tall-columnar cells with nuclear pseudostratification and papillary growth lined by non-mucinous cells.

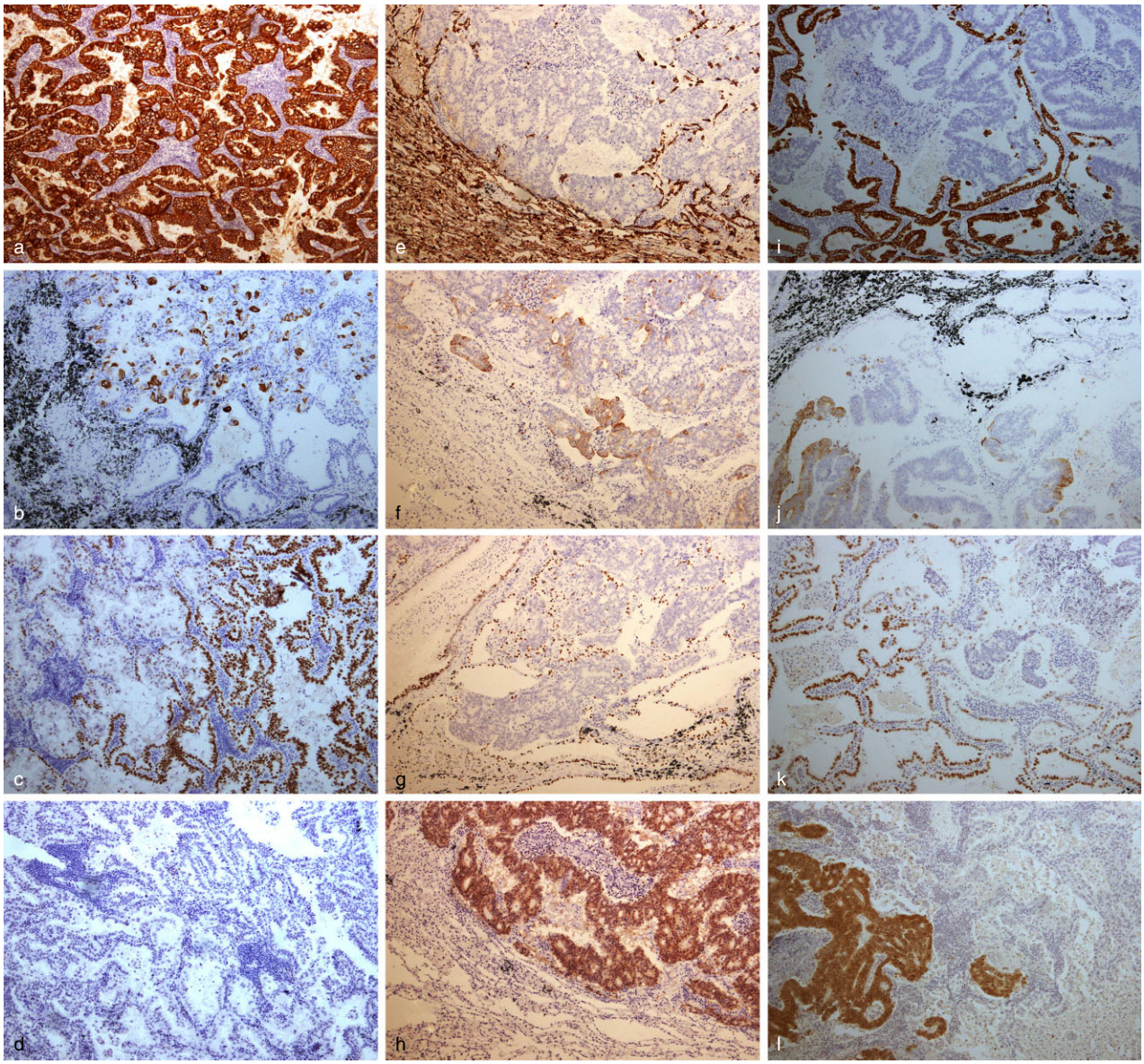

Figure 3 Immunohistochemistry phenotype of the three tumors (original magnification ×100): (**a–d**) *Nodule in the left upper lobe.* (a) Both mucinous and non-mucinous cells were diffusely positive for cytokeratin (CK)7. (**b**) Mucinous cells (up) were focally positive and non-mucinous cells (down) completely negative for CK20. (**c**) Mucinous cells (left) were focally positive and non-mucinous cells (right) diffusely positive for thyroid transcription factor 1 (TTF-1). (**d**) Both mucinous and non-mucinous cells were completely negative for CDX-2. (**e–h**) *The bigger nodule in the right upper lobe.* (**e**) Tumor cells were completely negative for CK7; (**f**) focally positive for CK20; (**g**) completely negative for TTF-1; and (**h**) diffusely positive for CDX-2. (**i–l**) *The smaller nodule in the right upper lobe*. Immunostaining of the tumor cells in two components were different by (**i**) CK7; (**j**) CK20; (**k**) TTF-1; and (**l**) CDX-2.

Signaling, Danvers, MA, USA).[9] The tumor in the left upper lobe was positive for E746_A750 and the two tumors in the right upper lobe were negative for both E746_A750 and L858R by mutation-specific IHC (Fig 4).

Discussion

It is well known that lung adenocarcinoma is heterogeneous, showing a wide variety of histologic patterns and cellular morphology. In the international multidisciplinary classification of lung adenocarcinoma, the enteric variant is defined as pulmonary adenocarcinoma with enteric differentiated component exceeding 50%. The enteric pattern shares morphologic and immunohistochemical features with colorectal adenocarcinoma, which consists of glandular structures lined by columnar cells with nuclear pseudostratification, and shows at least one immunohistologic marker of enteric differentiation (CDX-2, CK20, or MUC2). In contrast to

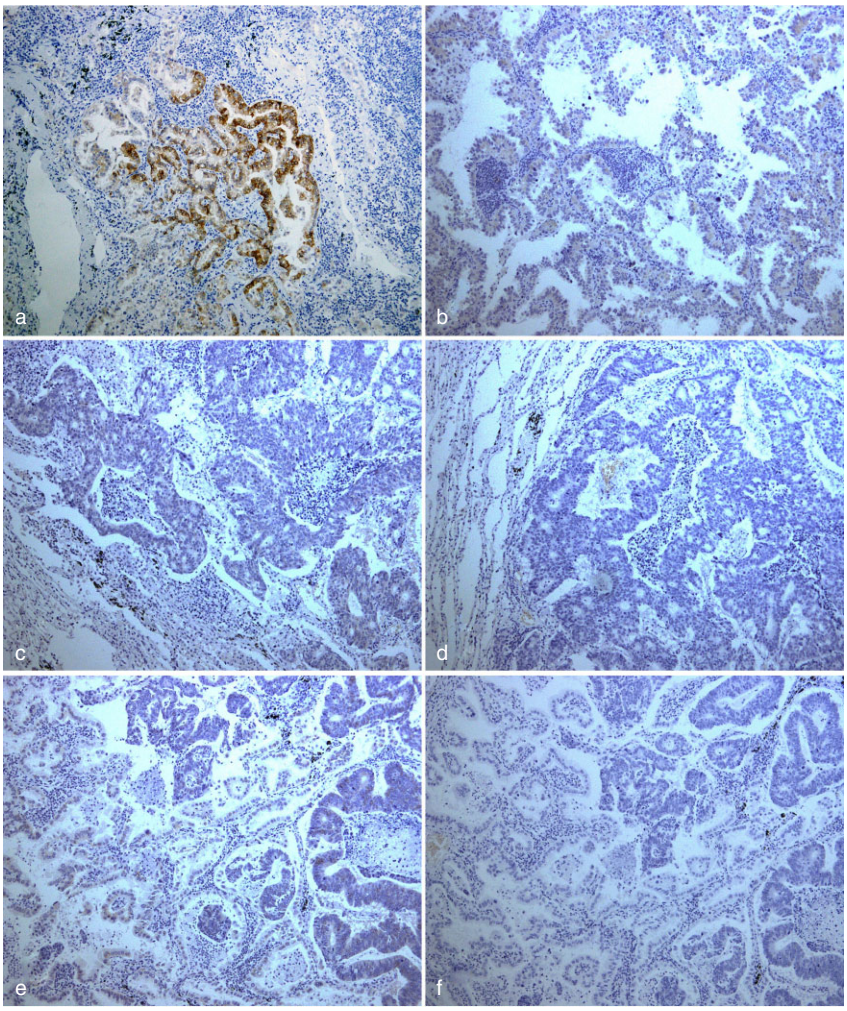

Figure 4 L858R and E746_A750del were detected by immunohistochemistry (IHC) using mutation-specific antibodies (original magnification ×100): (**a**,**b**) *Nodule in the left upper lobe.* (**a**) Tumor cells were positive for E746_A750del- specific IHC; and (**b**) negative for L858R-specific IHC. (**c**,**d**) *The bigger nodule in the right upper lobe.* (**c**) Tumor cells were negative for E746_A750del; and (**d**) L858R-specific IHC. (**e**,**f**) *The smaller nodule in the right upper lobe.* (**e**) Tumor cells were negative for E746_A750del; and (**f**) L858R-specific IHC.

metastatic colorectal adenocarcinoma, these tumors are histologically heterogeneous with some components that resemble primary lung adenocarcinoma, such as lepidic growth and immunohistochemically consistent positivity for CK7, and expression of TTF-1 in approximately half of the cases.[7] In our case, the larger nodule in the right upper lobe showed homogeneous features with enteric morphology and phenotype (CK7–/TTF-1–/CDX-2+/CK20+). The smaller one was heterogeneous, which consisted of an enteric pattern with phenotypes of CK7–/TTF-1–/CDX-2 + /CK20+ and lepidic/papillary patterns with phenotypes of $CK7^{+}$/$TTF\text{-}1^{+}$/$CDX\text{-}2^{-}$/$CK20^{-}$. Therefore, the diagnosis of metastasis of colon adenocarcinoma for the larger and colon adenocarcinoma metastasizing to lung adenocarcinoma for the smaller were concluded.

One of the major changes in the 7th Edition of the AJCC Staging Manual was the reclassification of cases with multiple nodules, which are considered as intrapulmonary metastases, rather than synchronous lung primaries (SLP). SLPs are defined as different histologic types or variation in growth patterns, cytology, and the absence of mediastinal lymph node involvement.[8] This is relatively easy to apply if the tumors are squamous, small or large cell, which are often morphologically uniform. However, in cases of adenocarcinomas, which are frequently histologically heterogeneous, this may be more complicated. A role for quantification of the relative amounts of morphologic subtypes in lung adenocarcinomas, as proposed by the international multidisciplinary classification of lung adenocarcinoma, as well as EGFR or KRAS mutation matches, has been suggested as a potentially useful method in

determining clonal relationships between the multiple nodules.[10] In our case, histologically, the tumor in the left upper lobe was composed of mucinous and non-mucinous cells growing in acinar (30%) and papillary (70%) patterns, while the pulmonary component of the colon adenocarcinoma metastasizing to lung adenocarcinoma in the right upper lobe was composed of non-mucinous cells growing in lepidic/papillary patterns. In addition, the former was positive for Exon 19 Del (E746-A750) and the latter was negative for both Exon19 Del (E746-A750) and Exon 21 (L858R) by mutation-specific IHC. For this reason, we considered the lung adenocarcinoma in the left upper lobe and the pulmonary component of the colon adenocarcinoma metastasizing to lung adenocarcinoma in the right upper lobe as SLP and favored the possibility of pT2a(2), rather than pT4.

Finally, the phenomenon of tumor-to-tumor metastasis has been described in literature for many years since Fried published the first documented case of bronchogenic carcinoma metastatic to a meningioma in 1930; however this remains fairly uncommon.[11] So far the limited reports have shown that renal cell carcinoma is the most common recipient among malignant tumors and lung cancer is the most frequent donor.[12] The reason for and mechanism of tumor-to-tumor metastasis are still unclear. The seed-and-soil theory possibly explains the underlying cause by correlating the relationship of the tumor cell and its microenvironment. As a result of the advancement of molecular biology, numerous molecules and pathways have been proposed to explain site-specific metastasis, such as Kiss-1/metastatin for lung metastasis of melanoma.[13] We present a fairly rare case with lung cancer acting as the recipient of tumor-to-tumor metastasis. The genetic mechanism driving this uncommon phenomenon is unknown and worth studying in the future.

Disclosure

No authors report any conflict of interest.

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