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Case Report

Isolated sigmoid colon metastasis from lung micropapillary adenocarcinoma: a case report

Rixiang Wang[1], Kaitai Liu[2], Deng Pan[6], Feng Ren[3], Wei Cui[4], Jingbo Jiang[5], Shibo Wu[5]

Departments of [1]Pharmacy, [2]Radiation Oncology, [3]Medical Imaging, [4]Anorectum, [5]Respiratory Medicine, Lihuili Hospital, Ningbo Medical Center, Ningbo 315041, China; [6]Department of Diagnosis, Ningbo Diagnostic Pathology Center, Ningbo 315041, China

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Abstract: Lung cancer is a common malignant neoplasm that is prone to distant metastasis. Gastrointestinal metastasis from lung cancer is rather rare no matter what stage. Herein, we presented a case of pulmonary adenocarcinoma six months after thoracoscopic Lobectomy isolated metastasis to sigmoid colon. Then the patient underwent radical resection of metastatic tumors of sigmoid colon. The pathologic morphology and immunohistochemistry of lung adenocarcinoma is highly consistent with the sigmoid colon tumor and their gene profiles are likely similar expect for an AXIN1 mutation in primary tumor and not in the metastatic lesion.

Keywords: Micropapillary, lung cancer, sigmoid metastasis, genetic profiles

Introduction

Lung cancer is the leading cause of cancer related deaths worldwide. One half of the disease with prior diagnoses have distant metastasis. The most common metastasis sites include the lungs, liver, bone, brain, and adrenal glands [1]. Gastrointestinal (GI) metastasis from lung cancer is considered rare, although there is about 4.7%-14% prevalence at autopsy [2, 3]. Due to a lack of pathology and molecular detection, lung cancer with GI metastasis is reported to have a poor prognosis with a mean survival of only 4-8 weeks [4].

Herein, we describe a case of lung adenocarcinoma characterized by partial micropapillary component, parabronchial lymph node metastasis, and lymphovascular infiltration six months after lobectomy, presenting as isolated metastasis sigmoid colon lesion. The morphology and immunohistochemistry of the primary are highly consistent with the metastasis sigmoid colon tumor. The two tumors shared similar gene profiles of EGFR exon 19 deletion mutations, the frameshift mutation of ARID1A 8 exon, and the missense mutation of SMAD4 9 exon expect for AXIN1 mutation only in the primary tumor.

Case presentation

In December 2017, a 47 year old non-smoking, otherwise healthy female was admitted to our hospital due to a nodule on the left upper lung, found in her physical checkup. Chest contrast enhanced computed tomography (CT) revealed an irregularly mixed-ground-glass nodule with the whole lesion sized 3.5 × 3.1 cm and the solid portion sized 2.1 × 1.3 cm in diameter was observed on apicoposterior segment of the left upper lung. The lump presented with lobulated, vacuolar, and pleural traction signs. Slight to moderately enhancement of the solid portion and no mediastinal lymphadenopathy was also revealed (**Figure 1A**, **1B**). Cranial contrast enhanced magnetic resonance, abdominal ultrasonography, and emission computed tomography of bone scan indicated no neoplasm dependent signs.

She was treated with thoracoscopic left upper lobectomy and mediastinal lymph node dissection. Postoperative pathology indicated invasive adenocarcinoma with 2.4 × 1.6 × 1.6 cm in diameter which was mainly composed of papillary type (**Figure 1E**), and the minor compositions of micropapillary type (**Figure 1F**) and aci-

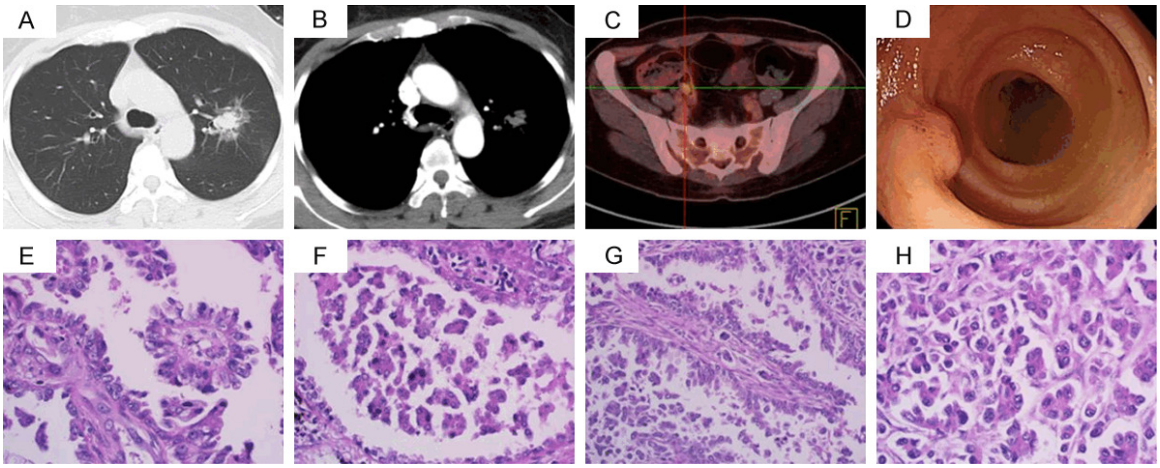

Figure 1. Chest computed tomography showed the primary tumor in the upper lobe of the left lung in the (A) Pulmonary and (B) Mediastinal windows. (C) Positron emission tomography-computed tomography (PET-CT) indicated increased fluorodeoxyglucose (FDG) uptake in the sigmoid colon. (D) Electronic colonoscopy images showed a 1.0 × 1.0 cm lump in the sigmoid colon that exhibited a rough mucosal membrane on the top, with clear boundaries. (E) Poorly differentiated invasive adenocarcinoma manifested as papillary subtype [hematoxylin eosin (H&E) × 40]. (F) poorly differentiated invasive adenocarcinoma manifested as micropapillary subtype (HE × 40). (G) Poorly differentiated adenocarcinoma metastatic to the sigmoid colon manifested as papillary subtype (HE × 20). (H) Poorly differentiated adenocarcinoma metastatic to the sigmoid colon manifesting as micropapillary subtype (H&E × 40).

nar type. Lymphovascular invasion was positive, perineural invasion was negative, and the tumor was close to pleura. Lymphatic metastasis was found in 1 of the 2 parabronchial lymph nodes and none of the dissected group 7, 10, 11 lymph nodes. Immunohistochemistry showed that the carcinoma cells were positive for CK7, Napsin A, SP-A and TTF1 (strong positive), Carcinoembryonic antigen (CEA) (focally positive), and negative for CK20, CDX2. TNM was defined as T1cN1M0 and she was diagnosed with primary adenocarcinoma of the lung stage IIB (according to the eighth edition of TNM classification of pulmonary carcinoma). According to guidelines, the patient received 3 cycles of 500 mg/m^2 pemetrexed on day 1 and carboplatin AUC 5 on day 1 every 3 weeks. Subsequently, chemotherapy was aborted because of liver dysfunction and intolerance.

Chest and abdomen CT surveillance were performed 3 months after chemotherapy, indicated an isolated lesion of sigmoid. Colonoscopy revealed sigmoid colon focal ulcerative lesion with a diameter of approximate 1 cm (**Figure 1D**). Pathologic findings of biopsy showed a poorly differentiated adenocarcinoma with prominent composition of papillary type. Immunohistochemical staining was consistent with intestinal metastasis of lung cancer. Positron emission tomography computed tomography (PET-CT) examination revealed an abnormal fluorodeoxy glucose (FDG) metabolism nodule in the sigmoid wall with the maximum standardized uptake value (SUV) value of 8.9 (**Figure 1C**). The patient underwent radical resection of sigmoid tumors in May 2018. Postoperative lesion sampling was macroscopically characterized as a 0.7 × 0.7 cm local mucosa rough area no higher than the mucosal surface in sigmoid with no myometrium involvement, gray-yellow cut section, and medium texture. Microscopic pathological findings suggested poorly differentiated invasive adenocarcinoma cancer from mucosal layer to muscular layer whose pathological subtypes are similar to those of previous lung cancer (**Figure 1G**, **1H**). Positive for lymphovascular invasion, negative for perineural invasion and four of nine peri-intestinal lymph nodes infiltrated by cancer cells were also observed. Immunohistochemistry showed that the carcinoma cells were positive for CK7, napsin A, SP-A and TTF1 (strong positive), carcinoembryonic antigen (CEA) (focally positive), and negative for CK20 and CDX2. Thus, the patient was diagnosed with sigmoid colon metastasis of lung adenocarcinoma.

Capture-based ultra-deep targeted NGS (Burning Rock, Guangzhou, China) was synchronously performed on lung primary tumor and sigmoid metastasis tumor tissue biopsy using a

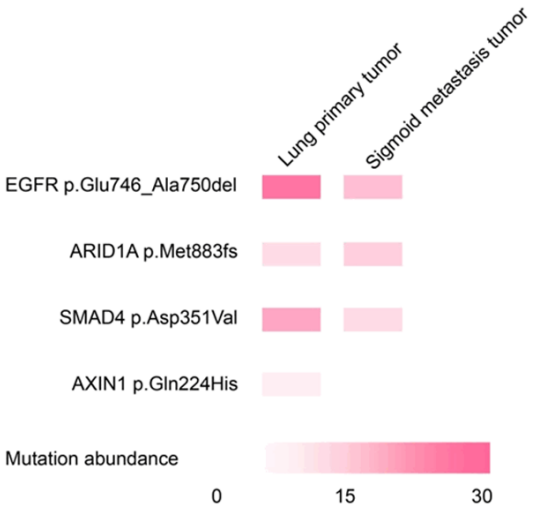

Figure 2. Somatic mutation matrix of genes screened using a panel consisting of 520 cancer-related genes. Each solid bar in the matrix represents a somatic mutation of a gene (row) in the specific tumor tissue specimens (column). Alternative mutation abundances (allele fractions) of somatic mutations are labelled with a different color depth, as indicated by the color key at the bottom of the figure.

panel consisting of 520 cancer-related genes, spanning 1.6 MB of human genome. Our data revealed the presence of EGFR exon 19 del in both specimens and the abundance of this mutation was 27.40% and 13.11%, respectively. The frameshift mutation (p.Met883) of AT-rich interactive domain 1A (ARID1A) 8 exon and the missense mutation (p.Asp351Val) of SMAD family member 4 (SMAD4) 9 exon were also found in both specimens, with the abundance of 6.75%, 9.45% and 17.46%, 7.18%, respectively. However, the AXIN1 missense mutation (p.Gln224His) was only detected in lung primary tumor (**Figures 2**, **3**). The tumor mutation burden (TMB) was 2.4/Mb in lung primary tumor and 1.6/Mb in sigmoid metastasis tumor. PD-L1 expression was assessed by using the anti-PD-L1 antibody (SP142, VENTANA, Roche). Immunohistochemical (IHC) with a negative result (0%).

Then the patient received gefitinib 250 mg per day for 8 months till now and no recurrence or metastasis lesion has been found by colonoscopy and enhanced chest and abdomen CT at every 3 months.

Discussion

We present a rare case of isolated sigmoid metastasis from adenocarcinoma of the lung diagnosed six months after lobectomy. As far as we know, this is the first reported case comparing the primary adenocarcinoma with the isolated sigmoid metastasis tumors in the pathologic morphology, immunohistochemistry and genetic profile in detail.

Gastrointestinal metastasis from lung cancer is considered to be rare, although there is about 4.7%-14% prevalence at autopsy [2, 3]. Yoshimoto et al. identified 56 (11.9%) cases in 470 patients with gastrointestinal metastasis confirmed by autopsied [5]. Kim et al. reported the incidence of the intestinal metastasis from lung cancer is as low as 0.2-1.7% [6].

Immunohistochemistry is an effective method to differentiate primary or metastatic pulmonary adenocarcinoma. The immunohistochemical markers of TTF-1, CK-20, CK-7, and CDX-2 are vital to identify origin from lung or intestinal tumors [7]. In our case, the morphology and immunohistochemistry of lung tumor is highly consistent with the sigmoid colon tumor. All the immunohistochemical markers supported their origin from lung. Moreover, both of the tumors sharing similar gene profile proved the homology of the two neoplasms from lung.

Why the pulmonary adenocarcinoma first developed isolated metastasis to the sigmoid remains uncertain. Miyoshi et al. noted that micropapillary pattern adenocarcinomas may have reduced cell adhesion, which is one reason why adenocarcinomas with micropapillary components are more metastatic and have a poor prognosis [8]. Xie et al. revealed that patients with EGFR 19 del are associated with more advanced disease which was not observed in patients with EGFR L858R, suggesting EGFR 19 del is a stronger oncogenic driver [9]. As our case is concerned, component of micropapillary type, lymphovascular invasion, parabronchial lymph node metastasis, and EGFR 19 del may suggest that the tumor is prone to distant metastasis. ARID1A, SMAD4, and AXIN1 recognized as tumor suppressor genes were found detectable mutations on NGS in the case. It has been shown that ARID1A mutations correlate closely with loss of ARID1A protein expression [10]. Decreased ARID1A protein expression in NSCLC tissues compared with normal bronchial epithelium was significantly correlated with poor tumor differentiation, tumor, node, metastasis (TNM) stage, and nodal status [11]. SMAD4 deficiency activated

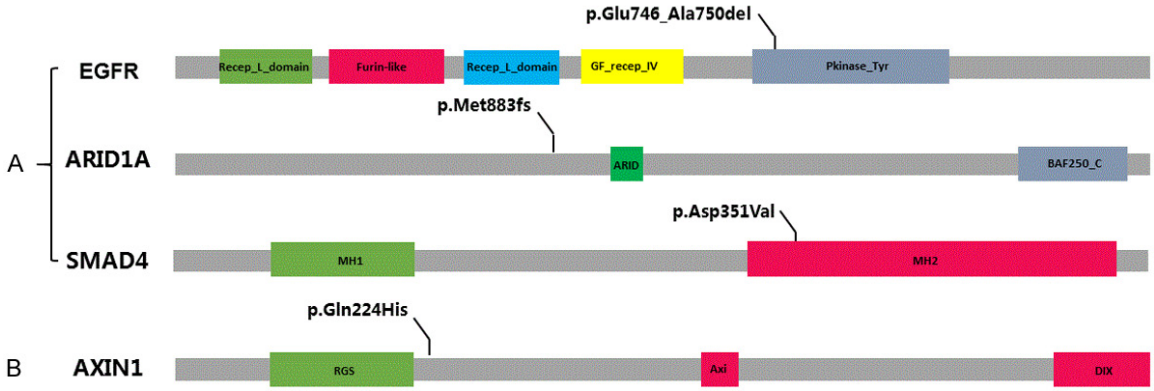

Figure 3. Genomic organization of somatic alterations identified in our patient. A. Alterations presence in both tumor tissue specimens. In EGFR, a deletion mutation lying in exon 19, which affects the protein tyrosine kinase domain; In ARID1A, a frameshift mutation lying in exon 8, which will in general cause the reading of the codons after the mutation to code for different amino acids; In SMAD4, a missense mutation lying in exon 9, and the accordingly changed amino acids located in the protein MH2 domain. B. Alteration only presence in lung primary tumor. In AXIN1, a missense mutation lying in exon 2, and the accordingly changed amino acids located between the RGS domain and Axin beta-catenin binding domain.

ERBB2 and AKT signaling pathways can ultimately promote lung cancer growth and metastasis in mouse model [12]. Mutations of AXIN gene have been detected in a few types of malignant tumors and these sporadic mutations hardly explain the reduced expression of AXIN which directly correlates with disease progression and poor prognosis [13]. As narrated above, the frame shift mutation of ARID1A 8 exon, the missense mutation of SMAD4 9 exon, and the AXIN1 missense mutation may also play a role in tumor metastasis.

In conclusion, lung carcinoma presenting with gastrointestinal metastasis is rather rare even at advanced stages. In our case, the morphology and immunohistochemistry of the primary were highly consistent with the metastatic tumor. The gene profiles are likely similar between the two except for AXIN1 mutation in the primary tumor which is not in the metastatic lesion. Components of micropapillary type, lymphovascular invasion, parabronchial lymph node metastasis, EGFR 19 del, ARID1A, SMAD4, and AXIN1 mutation may play a key role in tumor metastasis.

Disclosure of conflict of interest

None.

Address correspondence to: Shibo Wu, Department of Respiratory Medicine, Lihuili Hospital, Ningbo Medical Center, No. 57, Xing'ning Road, Ningbo 315041, China. E-mail: woshibo@yeah.net

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