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A case report of successful diagnosis of a pulmonary nodule by a survey of oncogenic mutations; primary lung carcinoma or pulmonary metastasis?

Akira Haro [a,*], Erina Kuramitsu [a], Ichiro Yamamoto [b], Yasuro Fukuyama [a]

[a] Department of Thoracic Surgery, Nakatsu Municipal Hospital, Nakatsu Municipal Hospital, 173 Shimoikenaga, Nakatsu, Oita 871-8511, Japan
[b] Department of Diagnostic Pathology, Nakatsu Municipal Hospital, Nakatsu Municipal Hospital, 173 Shimoikenaga, Nakatsu, Oita 871-8511, Japan

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ABSTRACT

INTRODUCTION: The number of patients diagnosed with solid carcinomas is increasing, and the most common site of metastasis is the lungs. It is often difficult to make a differential diagnosis between primary lung carcinoma and metastatic lung tumor in using histological examination and by determining their immunohistological status.
PRESENTATION: A 64-years-old man presented with dyspnea with chest computed tomography (CT) findings of a pulmonary tumor, and afterwards suffered from a sudden bowel hemorrhaged due to colorectal carcinoma. The histological diagnosis of a pulmonary tumor was poorly differentiated adenocarcinoma. Both Thyroid transcription factor-1 (TTF-1) and Cytokeratin20 (CK20) were immunohistologically negative. Of the some oncogenic mutations investigated, a neuroblastoma RAS viral oncogen homolog (NRAS) codon13 G13D mutation was detected in both the colorectal carcinoma and the pulmonary tumor tissue samples. Based on the result, the pulmonary tumor was diagnosed as a metastasis derived from colorectal carcinoma.
DISCUSSION: Recently, examination of the oncogenes of solid carcinomas has been clinically investigated in primary lung caricnoma and in colorectal carcinomas. The clinical advantage of the oncogenic mutation survey is to identify the site, and the type, of amino acid change in detail. This case is a rare successful case of a survey of the oncogenes for giving a differential diagnosis.
CONCLUSION: A survey of the oncogenic genes is very useful to make a differential diagnosis between primary lung carcinoma and metastatic lung tumor.

1. Introduction

The number of patients diagnosed with solid carcinomas is increasing, and the most common site of metastasis is the lungs. It is often difficult to give a differential diagnosis between primary lung carcinoma and metastatic lung tumor [1], especially in the case of solitary pulmonary tumor with lymphadenopathy. In these cases, clinical diagnosis is made using histological examination of the tumor and by determining their immunohistological status using specific markers, such as TTF-1. However, both diagnostic methods are inexact, and so, most patients with undifferentiated pulmonary tumors are treated using empirical chemotherapy regimens.

Recently, examination of the oncogenes of solid carcinomas, including primary lung carcinoma, has been undertaken. Epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma recptor (ALK) rearrangement has been clinically investigated in primary lung adenocaricnoma, and the Kirsten rat sarcoma viral oncogen homolog (KRAS) and NRAS mutations have been investigated in colorectal carcinomas. As such, patients with wild KRAS benefit from treatment using anti-EGFR therapies, such as panitumumab or cetuximab [2]. In the present case study, we present a case of successful diagnosis of a metastatic lung tumor derived from colorectal carcinoma by a survey of the oncogenic gene, NRAS.

2. Case report

A 64-years-old man presented with dyspnea. He had acute cardiac insufficiency, and chest X-ray and chest CT showed cardiac dilatation and a right side pulmonary tumor with right mediastinal and hilar lymphadenopathy and bilateral pleural effusion. Following his recovery from the acute cardiac insufficiency, he suffered from a sudden bowel hemorrhaged due to colorectal carcinoma (Fig. 1). The hemorrhage was locally controlled using radiation therapy (40 Gy/16 Fr) combined with oral S-1. After recovery from the heart failure and bowel hemorrhage, chest CT revealed that the size of the pulmonary tumor had increased in size to 10.4 cm

* Corresponding author.
E-mail address: aharo@surg2.med.kyushu-u.ac.jp (A. Haro).

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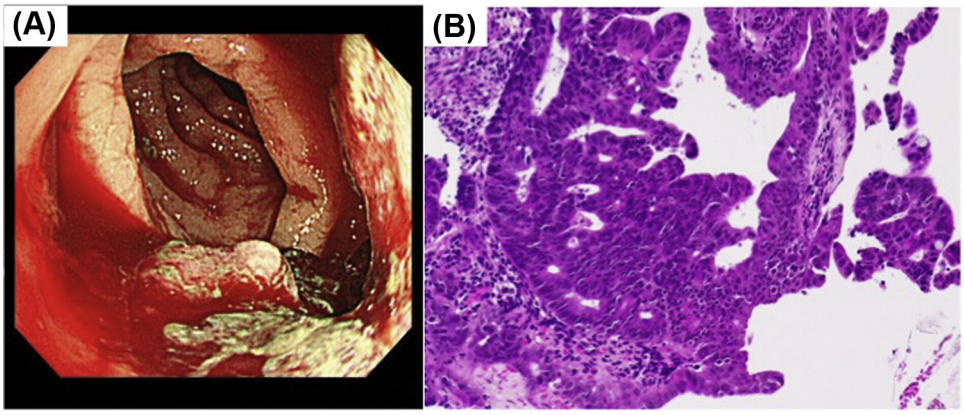

Fig. 1. Panel A: Colonoscopy revealed a bowel hemorrhage from the colorectal carcinoma. Panel B: Hematoxylin-eosin stain showed well-to-moderately differentiated tubular adenocarcinoma. (×200).

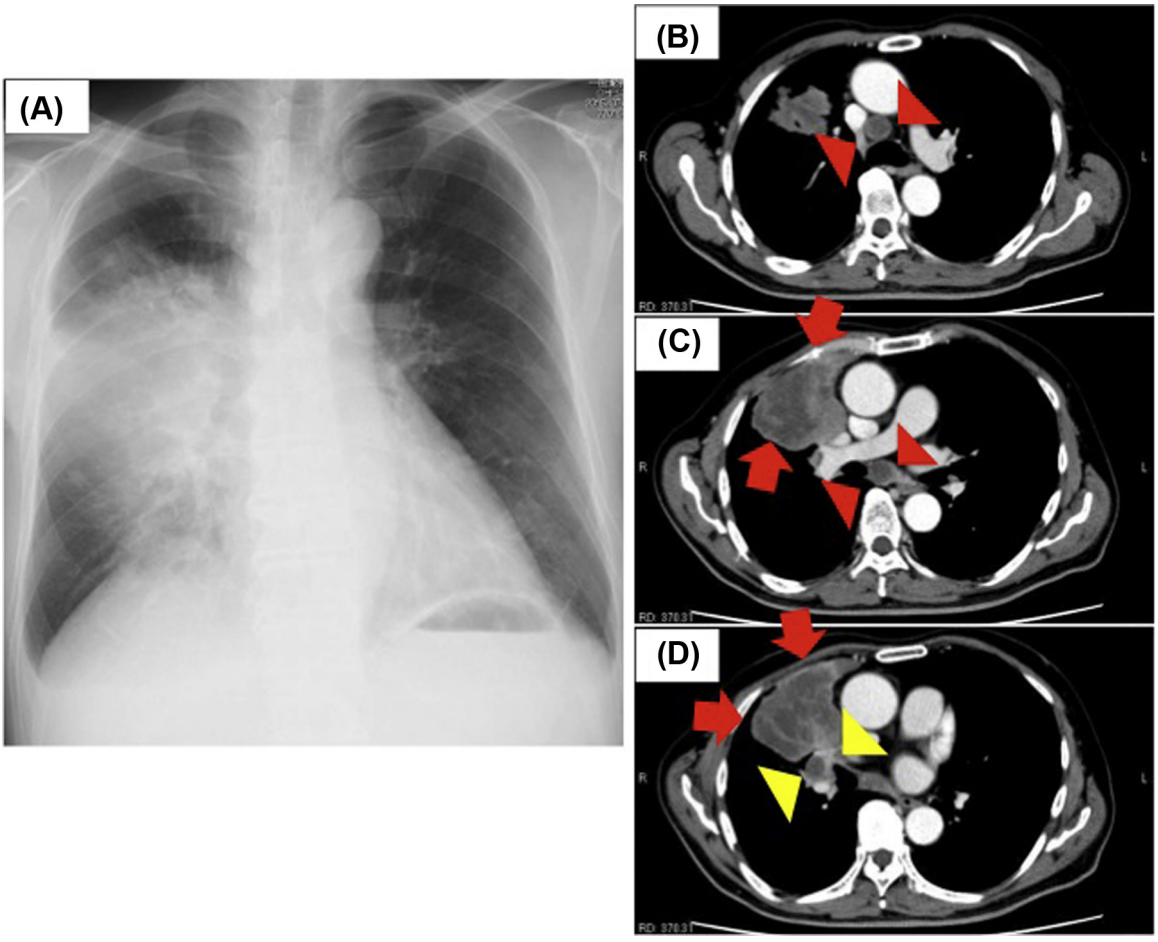

Fig. 2. Panel A: Chest X-ray revealed the right tumor and the infiltration shadows around the tumor. Panel B, and C and D: Chest CT revealed a pulmonary tumor(C and D; red arrows), hilar (D; yellow arrowheads) and mediastinal (B and C; red arrowheads) lymphadenopathy is enhanced by contrast medium.

(Fig. 2). A tissue biopsy of the pulmonary tumor was performed via bronchoscopy (Fig. 3A). The histological diagnosis was poorly differentiated adenocarcinoma (Fig. 3B). We could not make a differential diagnosis between primary lung carcinoma and metastatic lung tumor from colorectal carcinoma because both TTF-1 and CK20 were immunohistologically negative (Fig. 3C and D). As such, chemotherapy of carboplatin and irinotecan was given to the patient as irinotecan is effective for both primary lung carcinoma and colorectal carcinoma.

To make a more informed diagnosis, we furthermore investigated the EGFR mutation and ALK rearrangement of the primary lung carcinoma, and the KRAS and NRAS mutations of the colorectal carcinoma. Of the oncogenic mutations investigated, a NRAS codon13 G13D mutation was detected in both the colorectal carcinoma and the pulmonary tumor tissue samples. Based on the result, the pulmonary tumor was diagnosed as a metastasis derived from colorectal carcinoma. Four cycles of chemotherapy resulted in a partial response until a new bone metastasis appeared in the

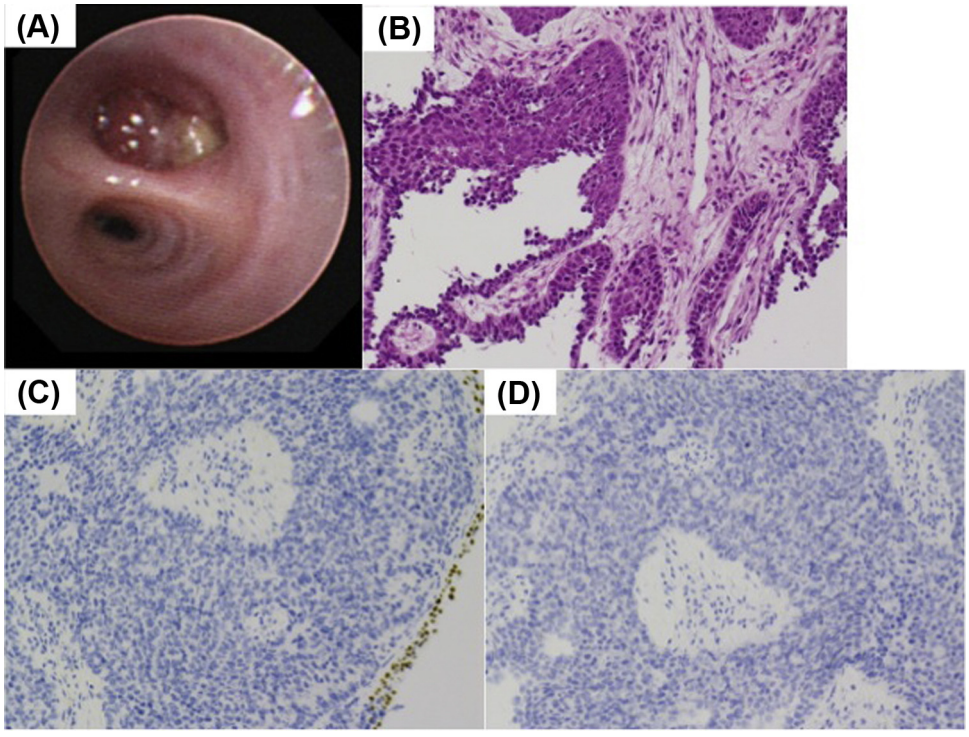

Fig. 3. Panel A: Bronchoscopy revealed the tumor in the segmental bronchus B5 of the right middle lobe. There was no finding of hemorrhage from the pulmonary tumor. Panel B: Hematoxylin-eosin stain shows poorly differentiated adenocarcinoma (×200). Panel C and D: Immunohistological staining showed that both TTF-1 (C) and CK20 (D) are negative in the pulmonary tissue sample (×200).

left iliac bone. After additional radiotherapy to the iliac bone for the relief of pain, the patient was administered bevasizmab and mFOLFOX6 for three cycles, which resulted in a diagnosis of stable disease.

3. Discussion

The number of patients with solid carcinomas is increasing, and one of the most common metastasis sites is the lungs. In the clinic, it is often difficult to differentiate between primary lung carcinoma and a metastatic lung tumor [1]. In these cases, clinical diagnosis is made based on histological examination of the tumor or by determining the immunohistological status of the tumor using specific markers, such as TTF-1. In the present case study, the immunohistological markers TTF-1 and CK20 were not useful in the diagnosis because the markers were negative in the pulmonary tumor. TTF-1 is negative in 15.5% of primary lung adenocarcinoma and positive in 87.5% of pulmonary metastatic adnocarcinoma [3]. In addition, the CK20 marker for colorectal carcinoma is negative in 40% of pulmonary metastasises derived from colorectal carcinoma [4].

Of the oncogenic mutations that were investigated, we found that the NRAS mutation was detected in both the colorectal carcinoma and pulmonary tumor tissue. From the frequency and sites of the mutations, and the amino acid changes of NRAS, we determined that the pulmonary tumor was a metastatic lung tumor arising from a colon carcinoma. The frequency of NRAS mutations in primary lung carcinoma is reported to be either 0.7% [5] or 0.5% [6], which makes it extremely rare. In contrast, the frequency of NRAS mutations is reported to be 2.6% in colorectal carcinoma [7]. In another study, the frequency of mutations was found to be 5.1% in colorectal carcinomas with wild-type KRAS codons 12 and 13 [8]. Of course, NRAS mutations are frequently observed in some solid carcinoma or hematological malignancies [9], and there is the possibility that both the colorectal carcinoma and the primary lung carcinoma might both contain NRAS mutation, but that they may no be derived from each other. However, it is more likely that the pulmonary tumor in this case was a pulmonary metastasis from the NRAS-positive colorectal carcinoma, because of the similarities in the NRAS mutations of both tumors. For colorectal carcinomas, the similarity of the KRAS and BRAF mutations between primary and metastatic tumor tissue samples was reported to be 100% [2]. In addition, we suggest that the advantage of the oncogenic mutation survey is to identify the site, and the type, of amino acid change in detail. For colorectal carcinoma, the nucleotide changes occur in codons 12,13 and 16, and the amino acid changes are Q61K/R/L, G12D/C/S and G13D [8] .In contrast, for primary lung carcinoma, the amino acid changes are Q61H/K/L/R (exon3), and G12A/C/D/R/S (exon2) [5]. CodonQ61 is the most frequent mutation of NRAS-positive primary lung carcinoma (81%), and around half of the mutation is in NRASQ61L [5]. To our knowledge, until now no study examining mutations in codon13 G13D has been reported.

RAS/RAF/MEK mutations are known to be mediators of acquired resistance in some solid tumors, such as: colorectal carcinoma, gastrointestinal stromal tumors, and melanoma. These type of cancer be responsive to targeted therapies [10], and there remains the possibility that the NRAS mutation in primary lung carcinoma might be a secondary mutation associated with resistance to drug therapy. However, the significance of NRAS varies between primary lung carcinoma and colorectal carcinomas. In a previous study that examined the frequency of secondary KRAS/KRAS/BRA/MEK1 gene mutations in primary lung carcinoma with acquired resistance to EGFR TKI [10], no NRAS, KRAS,or MEK1 mutations were detected, except for two cases of BRAF mutations [10] .For primary lung carcinoma, NRAS mutations are thought to be mutually exclusive with other known driver mutations, including EGFR, KRAS, and ALK [5], and they are thought to be one of the mechanisms of lung adenocarcinoma ontogenesis, even if it is a very rare event [6].

Currently, most patients with undiagnosed pulmonary tumors are treated with empirical chemotherapy regimens, and examination of the mutations in primary and pulmonary tumors is useful

in making an accurate diagnosis, and in selection of more effective treatment.

4. Conclusions

It is often difficult to differentiate between a primary lung carcinoma and a metastatic lung tumor. Examination of oncogenic mutations is a useful in the diagnosis of pulmonary tumors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Ethical approval

Not requested.

Consent

Written informed consent was obtained from the patients to publish this case report and the
accompaning images.

Author contribution

Akira Haro wrote the manuscript and is responsible for the imformation. Erina Kuramitsu, Ichiro Yamamoto and Yasuro Fukuyama reviewed critically the manuscript.

Guarantor

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