

CASE REPORT

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Peritoneum as the sole distant metastatic site of lung adenosquamous cell carcinoma: a case report

Pan Yang¹, Wei-Liang Li^{2*}, Jeff-X Zhou¹, Yu-Bo Yang³ and Xia-Xiang Jin⁴

Abstract

Background: Peritoneum metastasis of lung cancer is a rare event which, in addition to the peritoneum, usually involves multiple metastatic tissues. Here we report a case of a patient with lung adenosquamous cell carcinoma with the peritoneum as the sole distant metastatic site.

Case presentation: An 82-year-old Han Chinese man, in the teaching profession, was diagnosed with lung adenosquamous cell carcinoma in the upper lobe of his left lung with the involvement of ipsilateral hilar and mediastinal lymph nodes, and was initially staged as IIIa (cT₂N₂M₀). Molecular testing identified a mutation at *KRAS* G12A. Due to his poor physical condition, our patient was given gamma knife radiotherapy with a total dose of 28.0 Gy. Two weeks later, our patient was diagnosed as peritoneal metastasis identified by using magnetic resonance imaging and confirmed with ascitic cytology and peritoneal histology. No other distant metastatic sites such as liver, brain, bone, paranephroi, and lungs were found. Subsequently, our patient received palliative intraperitoneal chemotherapy, and died within 2 months.

Conclusions: Our patient represented a rare case of lung adenosquamous cell carcinoma harboring the *KRAS* G12A mutation, which metastasized distantly to the peritoneum only, and progressed rapidly.

Keywords: Lung adenosquamous cell carcinoma, Peritoneum, Metastasis, *KRAS* mutation

Background

Metastasis is the predominant cause of cancer-related death. For lung cancer, 40–60% patients have metastasis at diagnosis [1]. The most common metastatic sites for lung cancer include the brain, bone, and liver, among others [2]. The incidence of peritoneal metastasis of lung cancer is less than 5% [3, 4]. For lung cancer patients with peritoneal metastases, the prognosis is poor with a overall survival time of usually less than 2 months [3–10]. Kirsten rat sarcoma (*KRAS*) gene mutation is one of the key drivers for lung cancer development [11, 12], and is detected in 6–30% of non-small-cell lung cancer (NSCLC) patients [11, 13–16]. Patients with *KRAS* mutations can easily develop metastasis, and usually have poor prognosis [12, 17–19]. In this study, we report an

uncommon case of a patient with lung adenosquamous cell carcinoma harboring *KRAS* G12A mutation with the peritoneum as the sole distant metastatic site.

Case presentation

An 82-year-old Han Chinese man, in the teaching profession, was admitted to our hospital for cough and bloody sputum. Our patient did not have fever, chest pain, dizziness, headache, nausea, or vomiting. He had been an ex-smoker for 30 years, had had hypertension for more than 60 years, and had a history of coronary heart disease with myocardial infarction 10 years earlier. A physical examination showed that his vital signs were stable without edema, cyanosis, or lymphadenopathy. Blood test results showed increases in the counts of white blood cells (WBC) and neutrophils. Serum levels of cytokeratin (CK)-19 fragment CYFRA21-1 and CA153 were 3.57 ng/mL and 47.2U/mL, respectively. A chest

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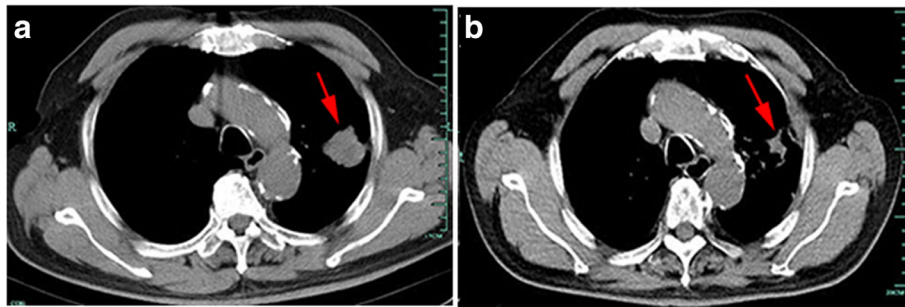


Fig. 1 **a** Chest computed tomography scan showed a mass in the upper lobe of the left lung (red arrow). **b** A chest computed tomography scan revealed that there was a reduction in the size of the mass in the upper lobe of the left lung after radiotherapy (red arrow)

computed tomography (CT) scan revealed a mass measuring 30 × 30 mm in size in the upper lobe of his left lung with an enlarged left hilum (Fig. 1a). A positron emission tomography-computed tomography (PET-CT) scan showed three hypermetabolic lesions in the upper lobe of his left lung, left hilum, and left mediastinal lymph node (Fig. 2). No distant metastatic sites such as liver, brain, bone, paranephroi, lungs, and peritoneum were found. Bronchoscopy revealed an external compression of the upper lobe of his left lung. A CT-guided percutaneous lung biopsy was carried out, and the histological examination showed adenosquamous cell carcinoma. Immunohistochemical (IHC) studies showed positive outcomes in thyroid transcription factor-1 (TTF-1), napsin-A (NAP-A), CK-7, and P63, and negative outcome in CK-20 (Fig. 3). Deoxyribonucleic acid (DNA) sequencing showed that the tumor harbored *KRAS* G12A mutation. Based on the clinical findings, our patient was staged as IIIa (T₂N₂M₀). Because of his poor physical condition, our patient was given palliative gamma

knife radiotherapy with a total dose of 28.0 Gy for one cycle combined with anti-infective therapy. The WBC count returned to the normal range and his vital signs were stable following treatment, and our patient was discharged at his request after hospitalization for 43 days. Ten days after discharge, he was admitted to the hospital again because of weakness and anorexia. Blood test results showed increases in WBC and neutrophil counts. Serum levels of CA125, CA199, and CA153 were 474.3U/mL, 467.5 U/mL, and 28.4 U/mL respectively. A chest CT scan revealed that there was a reduction in the size of the original tumor in the upper lobe of his left lung (Fig. 1b). Abdominal enhanced magnetic resonance image (MRI) analysis showed multiple nodule-like lesions in the hepatic capsule, and was considered as metastatic carcinoma in the peritoneum (Fig. 4). Peritoneal effusion and peritoneum biopsy were evidenced, and a cytological examination of the ascites found clustered and scattered tumor cells; IHC of peritoneum tissue and ascite tumor cells showed

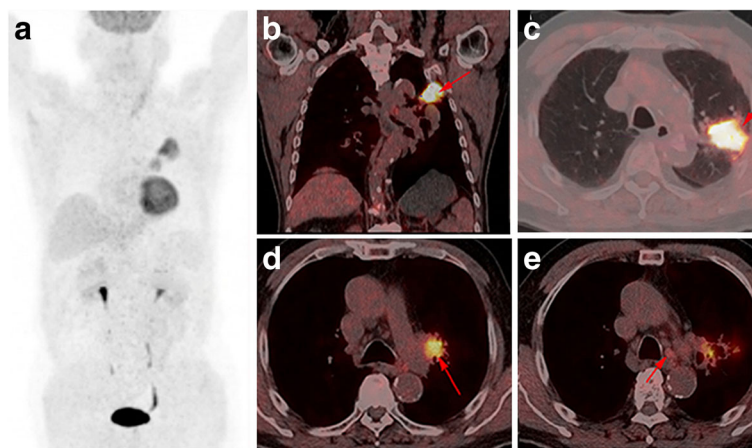


Fig. 2 **a** A positron emission tomography-computed tomography scan shows two hypermetabolic lesions in the upper lobe of the left lung and ipsilateral hilar lymph node. **b-c** Axial view of positron emission tomography-computed tomography scans for hypermetabolic lesion in the upper lobe of his left lung (red arrows), **d** in the left hilar lymph node (red arrow) and **e** in the left mediastinal lymph node (red arrow)

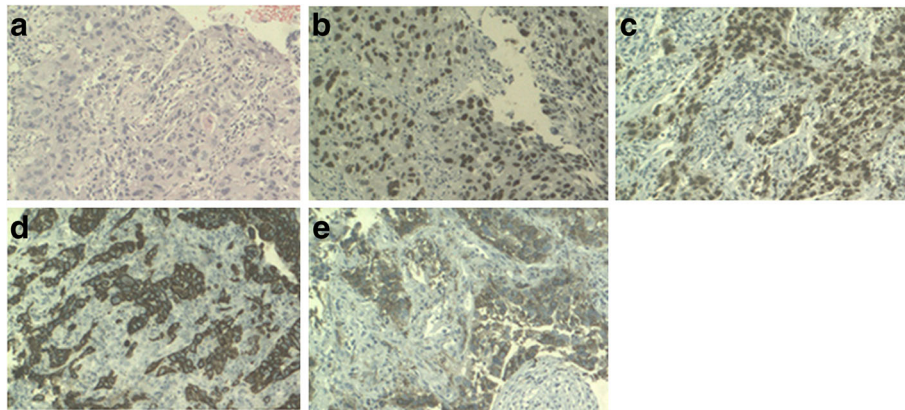


Fig. 3 **a** The tumor specimen shows adenosquamous cell carcinoma with moderate differentiation (hematoxylin and eosin staining, magnification $\times 40$). **b** Immunohistochemical of the tumor specimen is positive for p63 (positive in nucleus, magnification $\times 40$), **c** thyroid transcription factor-1 (positive in nucleus, magnification $\times 40$), **d** cytokeratin 7 (positive in cytoplasm, magnification $\times 40$), **e** napsin-A (positive in cytoplasm, magnification $\times 40$)

positive for CK-7 and TTF-1 (Fig. 5). No other distant metastasis was identified. Based on the progression of the disease, our patient was diagnosed with stage IV lung cancer with distant metastasis to the peritoneum (cT₂N₂M₁). Accordingly, our patient received palliative intraperitoneal chemotherapy (cisplatin 40 mg combined with recombinant human endostatin 45 mg) for one time. Unfortunately, no improvements were achieved and our patient died 11 days after readmission (Table 1).

Discussion

Peritoneum is a common metastatic site for gastric cancer [20], colorectal cancer [21], and ovarian cancer [22], but uncommon for lung cancer with its

incidence rate about 1–5% [3, 4]. In the reported cases involving peritoneal metastasis of lung cancer, there are usually multiple other distant metastatic tissues including brain, liver, and so on [4]. In the present case, it is reported as a lung adenosquamous cell carcinoma with peritoneal metastasis as the sole distant metastatic site, which was different from what was reported previously in which the pathological type included adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [3, 4].

The patient in the present case had rapid progression in his clinical course. There may be several reasons underlying the rapid progression of this disease. First of all, his general condition, including his age, hypertension, infection, and so on, had limited the treatment options. As a result, only palliative radiotherapy was administrated. Second, the pathological type of adenosquamous cell carcinoma may also have contributed to the rapid worsening of our patient's condition. It has been reported that adenosquamous cell carcinoma of the lung possesses strong invasion ability and usually metastasizes at an early stage [23–25], and peritoneal metastasis is usually followed by particularly poor prognosis [3, 4, 7]. The third, genetic alterations such as *KRAS* mutations can increase the activities of matrix metalloproteases, cysteine proteases, serine proteases, urokinase plasminogen activator, and enzymes responsible for tumor invasion and metastasis [26–28]. In the present case, the mutation in *KRAS* may have played a pivotal role in the metastasis of lung cancer. Li *et al.* reported a case of lung squamous cell carcinoma with *BRAF* V600E and *KRAS* G12A mutations with peritoneal metastasis [29]. In addition, Pal S et al.

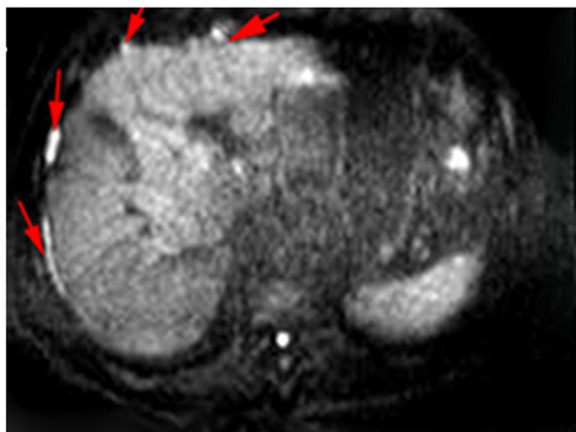


Fig. 4 Abdominal enhanced magnetic resonance image analysis showed multiple nodule-like lesions in the hepatic capsule (red arrows)

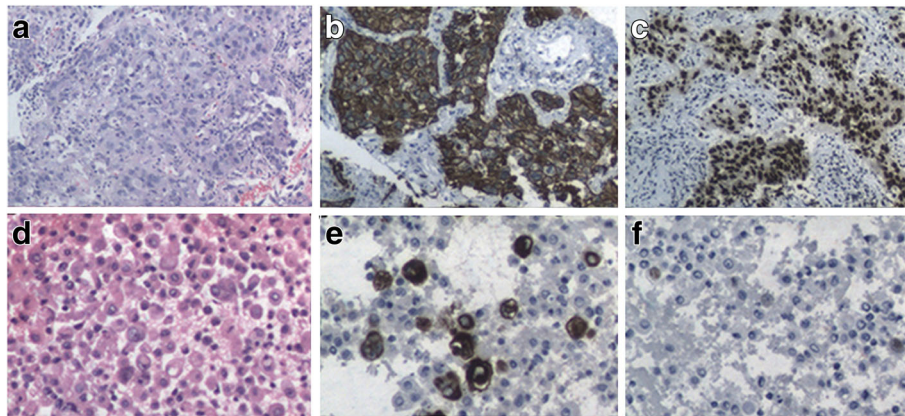


Fig. 5 **a** Cytological examination of peritoneum tissue (hematoxylin and eosin staining, magnification × 40). **b** Immunohistochemical of peritoneum tissue showed positive for cytokeratin 7 (magnification × 40) and **c** thyroid transcription factor-1 (magnification × 40). **d** Cytological examination of ascites tumor cells (hematoxylin and eosin staining, magnification × 100). **e** Immunohistochemistry of ascites tumor cells showed positive for cytokeratin 7 (magnification × 100) and **f** thyroid transcription factor-1 (magnification × 100)

reported that lung cancer with *KRAS* mutation had an increased incidence of distant metastasis [30].

Conclusions

In summary, according to the present case and reported literature, lung adenosquamous cell carcinoma with *KRAS* mutations has high susceptibility to distant metastasis including peritoneal metastasis and a very rapid progression of clinical course. Sometimes the

peritoneum may be the sole distant metastatic site and be followed by particularly poor prognosis.

Abbreviations

CA: Carbohydrate antigen; CK: Cytokeratin; CT: Computed tomography; CYFRA21-1: Cytokeratin 19 fragment; DNA: Deoxyribonucleic acid; Gy: Gray; IHC: Immunohistochemical; KRAS: Kirsten rat sarcoma; MRI: Magnetic resonance image; NAP-A: Napsin-A; NSCLC: Non-small-cell lung cancer; PET-CT: Positron emission tomography-computed tomography; TTF-1: Thyroid transcription factor-1; WBC: White blood cells

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Availability of data and materials

Not applicable.

Patient perspective

Not applicable.

Authors' contributions

PY followed up the patient, compiled the case details, and wrote the manuscript. W-LL, Y-BY and PY carried out the therapeutic regimen. W-LL reported on imaging and provided the CT/MRI figures. X-XJ reported on histology and immunohistochemistry and provided images for pathology figures. W-LL and J-XZ revised and restructured the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethical committee of Ningbo 113th Hospital of Chinese People's Liberation Army (PLA).

Consent for publication

Written informed consent was obtained from the patient's next-of-kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Table 1 Timeline of the patient

Dates	Course	Events
About Mar 28, 2016	At least day -10	Onset
Apr 7, 2016	Day 1	First hospitalization
Apr 12, 2016	Day 6	Bronchoscopy
Apr 15, 2016	Day 9	PET-CT
Apr 25, 2016	Day 19	Lung biopsy
May 6, 2016	Day 30	Gamma knife radiotherapy (started)
May 19, 2016	Day 43	Gamma knife radiotherapy (ended)
May 20, 2016	Day 44	<i>KRAS</i> G12A mutation reported
May 20, 2016	Day 44	Hospital discharge
May 30, 2016	Day 54	Readmission
May 31, 2016	Day 55	Peritoneocentesis
Jun 4, 2016	Day 59	MRI
Jun 6, 2016	Day 61	Peritoneal biopsy
Jun 8, 2016	Day 63	Intraperitoneal chemotherapy
Jun 10, 2016	Day 65	Died

PET-CT positron emission tomography-computed tomography, *KRAS* Kirsten rat sarcoma, *MRI* magnetic resonance imaging

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