Lymph node and bone metastasis of pulmonary intestinal adenocarcinoma: A case report

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Abstract. Pulmonary enteric adenocarcinoma (PEAC) is a rare pathological type of lung adenocarcinoma, accounting for ~0.6% of primary lung adenocarcinoma, which has similar morphological and immunohistochemical characteristics to colorectal adenocarcinoma. Making a certain differential diagnosis of PEAC based on morphological and immunohistochemical results is difficult. It is known that PEAC may metastasize to the pancreas, skin, soleus muscle and intestine, but no bone metastasis has been reported. At our department, a rare case of PEAC with bone and lymph node metastasis was previously diagnosed. The present case study reports on a 58-year-old male patient encountered at our hospital with pain in the lumbar, back and right iliac with no obvious cause. Chest CT indicated a space-occupying lesion in the left upper lung lobe, enlarged lymph nodes in the mediastinum and left lung, and partial vertebral bone destruction. Enhanced CT results indicated multiple foci of active bone metabolism in the body, while rectal colonoscopy showed no obvious abnormalities. Histopathological and immunohistochemical results after right iliac bone puncture suggested stage IV PEAC with secondary malignancies in bones, mediastinal lymph node, hilar lymph node and left supraclavicular lymph node.

Introduction

Pulmonary enteric adenocarcinoma (PEAC) is a rare primary lung adenocarcinoma with histological morphologies similar to those of metastatic colorectal cancer, but its etiology remains elusive. Severe intestinal lesions accompanied by necrosis patterns were observed in more than half of the cases reported (1,2), which expressed at least one of the typical immunohistochemical markers of intestinal differentiation, including caudal type homeobox 2 (CDX2), cytokeratin 20 (CK20) or mucin 2 (MUC2) (2-4). Another review including 127 patients showed that the median overall survival (OS) of patients with early PEAC was 56 months, while the median OS of patients with advanced or metastatic diseases was 14 months (5). PEAC is often difficult to distinguish from metastasis of colon cancer, so the differential diagnosis between these two types of cancer is a challenging clinical issue (6).

Secondary bone malignancies are usually caused by metastasis to the bone of other malignant tumors (7,8), while secondary lymph malignancies are more common in intermediate and advanced cancers. In the present case, it was hypothesized that the metastasis of the bone and lymphatic system was caused by deteriorated lung cancer. Of note, bone and lymphatic metastasis of PEAC are rare to be observed.

In addition, most of the previously reported PEACs are metastasized from colorectal cancer (6). However, in the present case, no abnormalities were found during colorectal examination, which means that this is a rare case of primary PEAC. There was no obvious discomfort in the early and middle stages of cancer.

Case report

A 58-year-old male, a long-term smoker with ~8 cigarettes per day, was admitted to the Department of Orthopedics of the Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) in December 2022 due to pain in the lower back and right iliac region with no obvious inductance. The patient denied any history of chronic diseases, including hypertension, coronary heart disease, diabetes, hepatitis, typhoid fever, malaria and other infectious diseases. The case information and images published in this case report were obtained with the patient's written informed consent.

Physical examination indicated the following: Positive for thoracolumbra spinous process tenderness, no abnormalities were found in the auscultation of the heart and lungs, abdominal signs and symptoms were negative and no abnormalities were found in the limbs and nervous system examination.

The first laboratory examination (blood sample) showed that carcinoembryonic antigen, carbohydrate antigen 125 (CA125) (1,250.00 U/ml; normal range, 0-24 U/ml) and CA72-4 (74.50 U/ml; normal range, 0-6.9 U/ml) were markedly

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increased, while neuron-specific enolase and non-small cell lung cancer-associated antigen (CYFRA) were also increased to a certain extent. In a repeat examination after 2 weeks, the above-mentioned indexes had further increased to varying degrees (CA125: 3,706.00 U/ml; normal range, 0-24 U/ml; CYFRA: 19.10 ng/ml; normal range, 0-3.3 ng/ml), while the level of CA72-4 had decreased (53.70 U/ml; normal range, 0-6.9 U/ml) (Table I).

Chest CT and enhanced CT revealed space-occupying lesions in the upper lobe of the left lung with enlarged lymph nodes in the mediastinum and left hilum, bone destruction in certain vertebral bodies, multiple nodules in both lungs, interstitial lesions in both lower lobes, fibrous foci in the lower lobe of the right lung and the upper lobe of the left lung, and localized thickening of the bilateral pleura (Fig. 1A-D). CT plain scan of the brain, liver, bile, pancreas and spleen showed no obvious abnormalities, while bone destruction was found in the right femur, left inferior rami of pubis, right ischial bone, right iliac bone, sacrum and a proportion of the lumbosacral vertebrae, and part of the lumbosacral vertebrae showed compact shadows.

Thoracic MR plain scan showed multiple abnormal signals in the thoracolumbosacral vertebra and certain adnexal areas, indicating the formation of metastatic foci (Fig. 1E-G).

In the early stage of treatment, it was planned to perform lung mass puncture biopsy on the patient, but the preoperative examination showed that the coagulation D-2 polymer was as high as 11,220 ng/ml (reference range, 0-1,000 ng/ml), a significant contraindication for puncture. In this case, according to the condition and imaging examination results, it was decided to puncture the iliac tissue instead of puncturing the left upper lobe tumor. CT-guided fine needle aspiration (FNA) and endoscopic ultrasound-guided FNA were performed to obtain the right iliac tissue tumor specimens, suggesting a metastatic adenocarcinoma.

Immunohistochemical test was performed according to standard procedures and results of iliac bone puncture tissues were found to be positive for CK7, CK19, CDX2, villin, tumor protein p53 (p53; 60%) and Ki-67 (70%), and negative for CK20, p16 (0%), transcription termination factor 1 (TTF-1), napsin A aspartic peptidase (NapsinA), prostate-specific antigen (PSA) and carbohydrate antigen 19-9 (CA19-9). All the antibodies were purchased from Xi'an Dingguo Trading Co., Ltd., dilutions were set at 1:100 according to the manufacturer's recommendations for immunohistochemistry for each antibody and all antibodies were rabbit anti-human monoclonal antibodies. Consecutive parallel sections were stained with the following antibodies: CK7 (cat. no. DG300545), CK19 (cat. no. DG300347), CDX2 (cat. no. DG300171), villin (cat. no. DG302057), p53 (cat. no. DG302700), Ki-67 (cat. no. DG300540), CK20 (cat. no. DG300366), p16 (cat. no. DG302620), TTF-1 (cat. no. DG300313), NapsinA (mouse anti-human monoclonal antibody; cat. no. DG169), PSA (cat. no. DG302428) and CA19-9 (mouse anti-human monoclonal antibody; cat. no. DG208). The test tissue was sliced into 5-μm thick sections and fixed at room temperature for 4 h using 10% neutral formalin. H&E staining was performed using standard reagents at room temperature for 7 min (hematoxylin staining for 5 min and eosin staining for 2 min; Guidechem). The patient was diagnosed with metastatic adenocarcinoma based on the histopathological and immunohistochemistry results, assessed using light microscopy at x400 magnification (Fig. 2).

Positron emission tomography/CT was performed to detect the tumor metabolic status. The metabolism level of ^{18}F-fluorodeoxyglucose was increased in the tubercle on the left superior lobe of the lung and the tubercle was considered to be a malignant tumor. Metastasis was observed in the left hilar lymph node and mediastinal lymph node, and multiple bone metastases were observed throughout the body. Multiple small nodules in both lungs showed no increase in glucose metabolism. The left adrenal junction was slightly thickened and no increase in glucose metabolism was observed. Soft-tissue masses had formed around multiple vertebrae of the neck, chest and lumbar spine and accessories, bilateral iliac crest and sacrum, and an increase of nuclide uptake was observed in these soft-tissue masses (Fig. 3). There was no obvious abnormality in the craniocerebral parenchyma.

To rule out the probability of colorectal adenocarcinoma, rectal colonoscopy was performed and no abnormalities were found.

To explore the mutant spectrum of tumor samples, consent from the patient was obtained to perform genetic analysis with next-generation sequencing, aiming to identify somatic variations among 571 cancer-associated genes, including epidermal growth factor receptor, ALK receptor tyrosine kinase, ROS proto-oncogene 1 receptor tyrosine kinase, ret proto-oncogene, KRAS proto-oncogene (KRAS) and KIT proto-oncogene. Genetic analysis of tumor samples was performed by Ide Medical Laboratory Ltd. using the Illumina NovaSeq 6000 platform (Illumina, Inc.). Of the 571 genes examined, only the KRAS and kelch-like ECH-associated protein 1 (KEAP1) genes were mutated. KRAS showed a missense mutation in exon 3 (c.183A> T, p.Q61H) and KEAP1 exhibited a frameshift mutation in exon 6 (c.1796del, p. S599Wfs*73) (Table II).

The final diagnosis of the patient with primary pulmonary intestinal adenocarcinoma was submitted to the oncology department of our hospital for subsequent treatment. However, due to personal reasons, the patient and their family decided to give up on subsequent treatment. The prognosis was extremely poor. Prior to this, a palliative treatment plan based on basic symptomatic and supportive treatment was carried out, including anticoagulant treatment, protein supplementation, amino acid supplementation, fat emulsion and electrolyte treatment. As the patient suffered from moderate to severe cancer pain, morphine and OxyContin were administered for pain relief. After follow-up investigations, the patient passed away ~3 months after discharge.

Discussion

According to the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma (9), PEAC is defined as a type of lung adenocarcinoma with enteral differentiation by >50%. This type of cancer frequently exhibits characteristics of colorectal adenocarcinoma, such as glandular, papillary and/or sieve structures with luminal necrosis, tall columnar cells with pseudostratification, atypical nuclei and eosinophil

Table I. Laboratory examination results at different time points.

Characteristics	First examination	At 2 weeks after the first examination	Reference value
CEA, ng/ml	185.00	500.00	0-5.00
NSE, ng/ml	16.40	24.80	0-16.3
CYFRA, ng/ml	7.51	19.10	0-3.3
CA125, U/ml	1255.00	3706.00	0-24
CA72-4, U/ml	74.50	53.70	0-6.9

CEA, carcinoembryonic antigen; CA, carbohydrate antigen; NSE, neuron-specific enolase; CYFRA, non-small cell lung cancer-associated antigen.

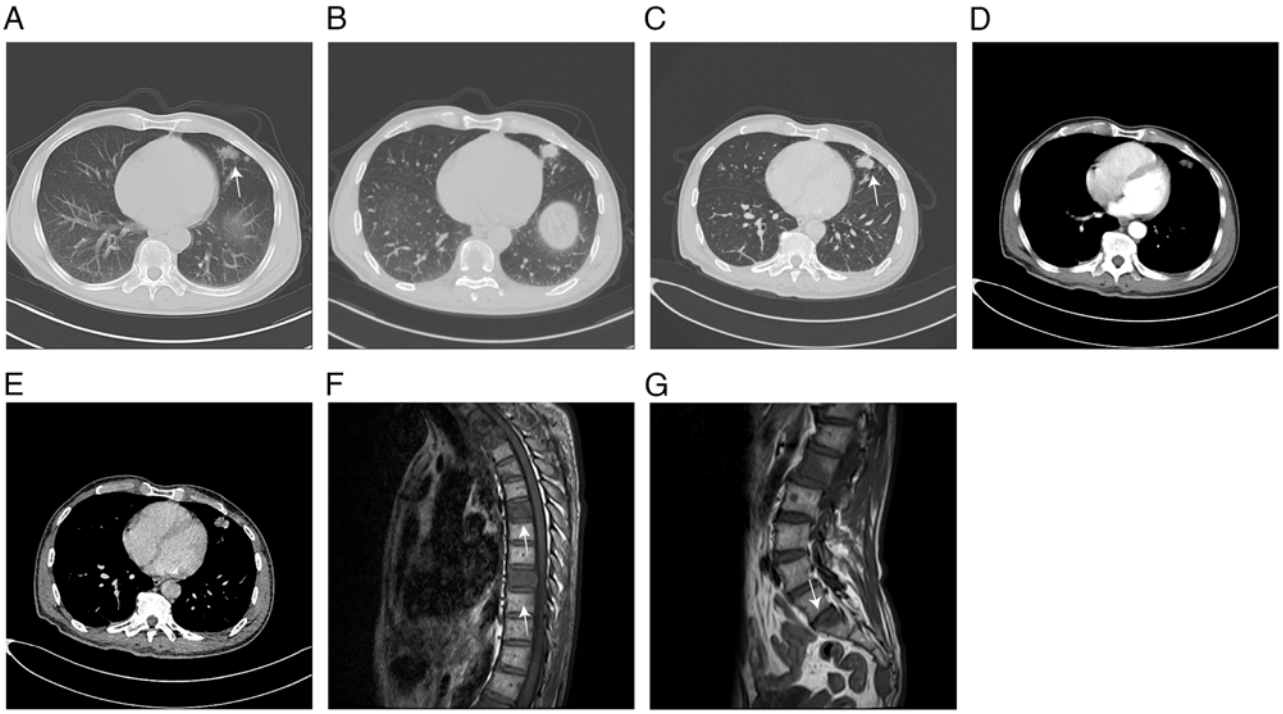

Figure 1. CT features of different organ lesions, MRI features of thoracic and lumbar vertebrae. Obvious lesions are indicated by white arrows. (A) Plain CT scan of the lung window showed space-occupying lesions in the left superior lingual segment of the lung. (B) Multiple nodules in both lungs, interstitial lesions in the lower lobes of both lungs, and vertebral bone destruction. (C) Contrast-enhanced window CT showed fiber foci in the upper lobe of the left lung. (D) Mediastinal window bilateral localized pleural thickening and multiple nodules in both lungs. (E) Mediastinal window enhanced scan. (F) MRI of the thoracic vertebra showed metastasis. (G) Lumbar spine MRI indicated metastasis.

cytoplasm, making PEAC difficult to be distinguished from colorectal adenocarcinoma (10,11). Currently, the differential diagnosis is mainly based on the combination of immunohistochemical markers. CK7 is positive in most PEAC cases and is often expressed in breast, endometrium, pancreas, biliary tract and lung tissues (12), but not in the gastrointestinal tract. TTF-1 and NapsinA are specific biomarkers of lung adenocarcinoma, which were reported to be generally positive in PEAC (13,14), while being negative in lung metastatic gastrointestinal adenocarcinoma. CDX2, CK20 and MUC2 are generally expressed in intestinal tissues, and at least one of them is positive in PEAC (15,16). However, PEAC cases with lung cancer-specific immunophenotypically negative status, such as negative results for TTF-1 and NapsinA, have been previously reported, suggesting that the understanding of PEAC remains incomplete (5).

The onset of PEAC is usually insidious and most patients have no specific clinical symptoms, which makes it difficult for patients to receive an early diagnosis and treatment; the condition has usually been developing for a period of time when admitted to the hospital, which may relate to the fact that PEAC mostly manifests as peripheral lung cancer that mostly originates from small bronchi and grows slowly (17-19). Zhao *et al* (20) summarized the clinical symptoms of 28 patients with primary PEAC. They determined that 42.9% of the patients initially presented with a cough, including 3 patients with cough accompanied by hemoptysis, 1 patient with cough and fever accompanied by chest and back pain, 1 patient with cough accompanied by fever, and 1 patient with persistent chest and back pain (20). In the case reported in the present study, the patient presented with advanced symptoms of distant metastasis at diagnosis,

Table II. Results of gene mutation analysis.

Gene	Exon	Nucleotide variation	Aminoacid variation	Variant allele frequency, %
KRAS	3	c.183A>T	p.Q61H	5.44
KEAP1	6	c.1796del	p.S599Wfs*73	4.60

KEAP1, kelch-like ECH-associated protein 1; KRAS, KRAS proto-oncogene.

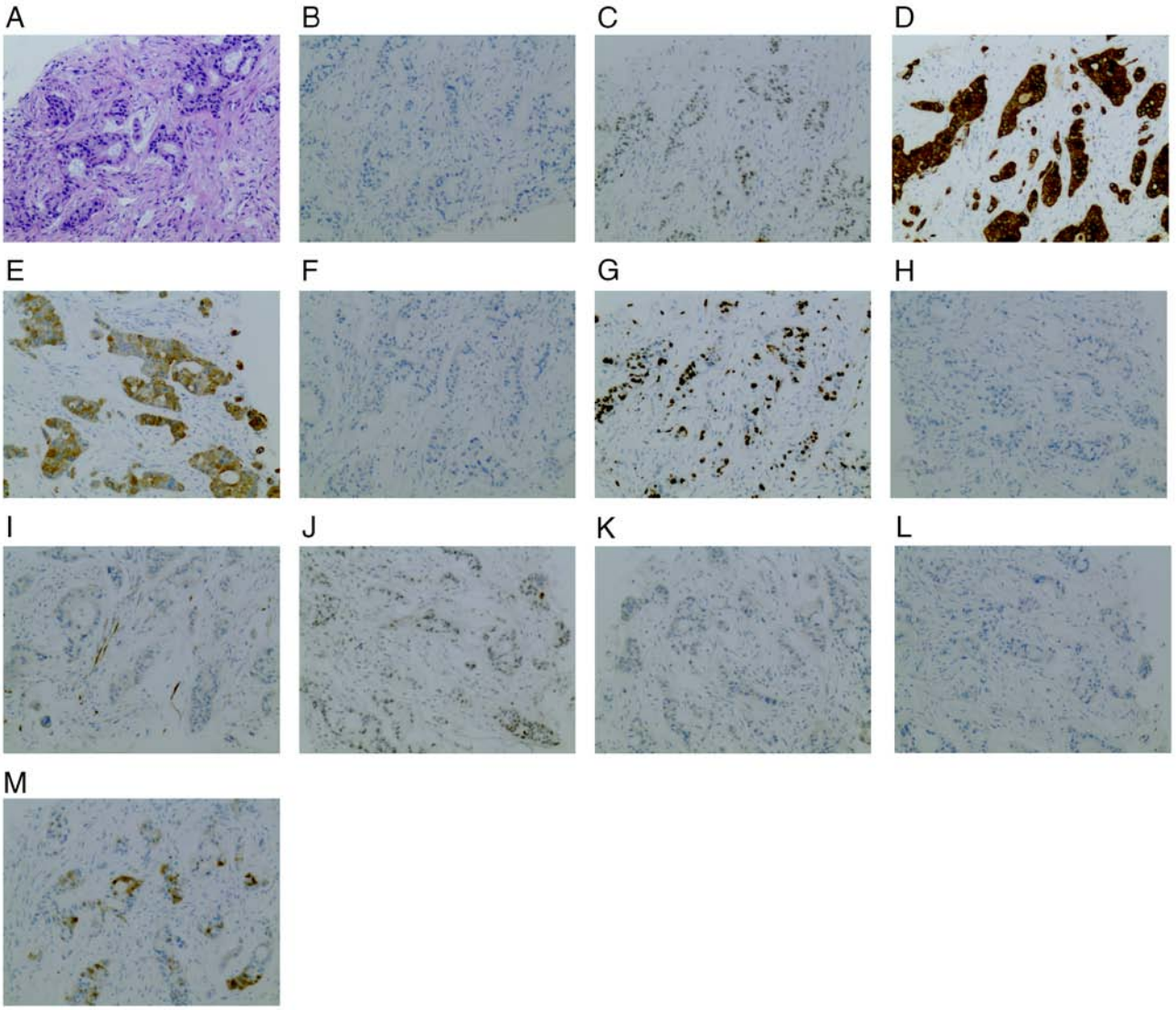

Figure 2. Immunohistochemistry and histopathology results of right iliac bone puncture tissue. (A) The histopathological section stained with H&E showed significant cell necrosis, which indicated metastatic adenocarcinoma. Immunohistochemistry indicated thetissues to be (B) carbohydrate antigen 19-9-negative, (C) caudal type homeobox 2-positive, (D) CK7-positive, (E) CK19-positive, (F) CK20-negative, (G) Ki-67-positive (70%), (H) napsin A aspartic peptidase-negative, (I) p16-negative (0%), (J) tumor protein p53-positive (60%), (K) prostate-specific antigen-negative, (L) transcription termination factor 1-negative and (M) Villin-positive (magnification, x100). CK, cytokeratin.

accompanied by multiple bone and lymphatic metastases, which is very rare in clinical practice, but no gastrointestinal symptoms were observed throughout the course of the disease and no abnormalities were observed under colonoscopy. Malignancies with lung metastasis not only show respiratory symptoms, but also exhibit symptoms associated with the primary disease, which may be distinguished from lung metastatic colorectal cancer (21).

The imaging findings of PEAC are different from those of typical invasive lung adenocarcinoma, in which the lesions are often larger, but there are no significant differences in the lobular sign, burr sign and pleural effusion, which manifest as patches, compact lesions or ground glass lesions (21). It is difficult to distinguish PEAC from the imaging perspective only, and histological and immunohistochemical phenotyping are also required. Immunohistochemical results are

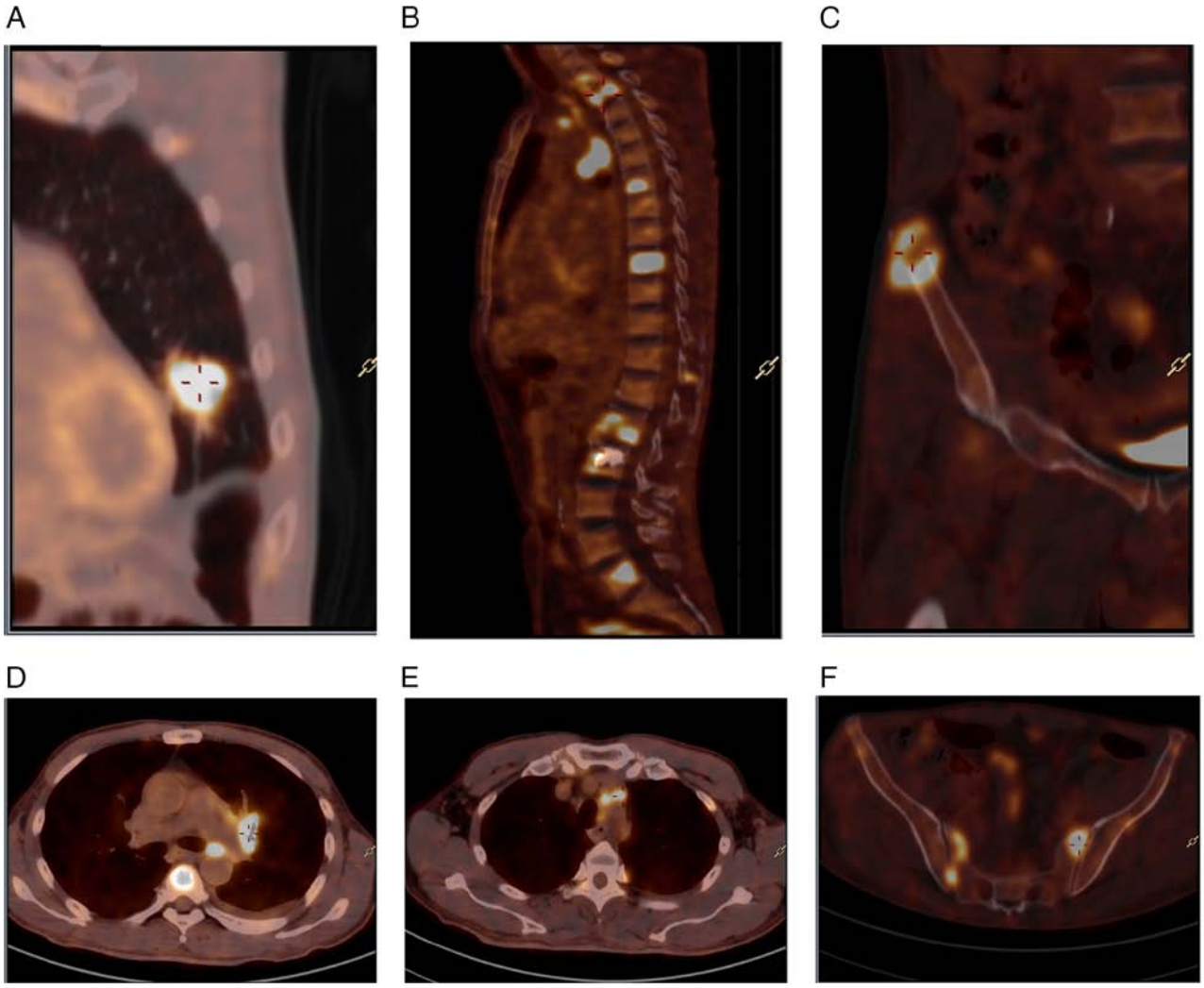

Figure 3. Characteristics of positron emission tomography/computed tomography lesions. (A) Increased uptake of ^{18}F-FDG in the tubercle of the left superior lingual segment, SUV max 16.6. (B) Increased uptake of ^{18}F-FDG in multiple vertebral bodies of neck, thoracic, lumbar vertebrae and accessories, SUV max 18.08. (C) Increased uptake of ^{18}F-FDG in iliac crest, SUV max 15.44. (D) Increased uptake of ^{18}F-FDG in left hilar lymph nodes, SUV max 13.08. (E) Increased uptake of ^{18}F-FDG in mediastinal lymph nodes, SUV max 8.97. (F) Increased uptake of ^{18}F-FDG in the sacrum, SUV max 16.73. FDG, fluorodeoxyglucose. SUV, standardized uptake value.

of great significance in the diagnosis of this disease, and in spite of its low incidence and the small number of cases, more efforts should be made to find specific diagnostic markers (22).

Previous studies have identified smoking as a predisposing factor for PEAC, and the WNT-SOX2 signaling regulation pathway is over-activated under the stimulation of smoking and other factors, which may lead to intestinal metaplasia of airway basal cells. However, a recent study suggested that smoking may not be an important risk factor for the development of PEAC (23). In addition, several studies have shown that males are more likely to have PEAC, while other studies have come to the opposite conclusion (24). These controversies may be related to the limited number of reported cases so far, which were not able to support such large-scale statistics and analysis. However, it is widely thought that most patients with PEAC are elderly individuals.

In previous studies, it was noted that the occurrence of PEAC is often accompanied by the mutation of KRAS (2,5,25). Furthermore, KEAP1, a drug-resistant gene mutation, was also found in the present case.

Of the 46 PEAC cases examined by Nottegar *et al* (26), more than half had KRAS mutations and similar results were found in a retrospective cohort study by Xie *et al* (27). The KRAS gene is a proto-oncogene in the RAS family (28) and the most frequently mutated sites are mostly concentrated in codon 12 of exon 2, accounting for 90% (29). In the present case, the KRAS gene mutation comprised a missense mutation of codon 61 in exon 3, which led to the mutation of amino acid 61 of the gene-encoded protein from glutamine to histidine. This mutation is located in the GTp-binding region of the KRAS protein, a hot spot mutation that leads to the decrease of KRAS GTase activity. It preferentially interacts with Raf-1 proto-oncogene and activates ERK signaling, leading to cell transformation (30).

KEAP1 binds to Nrf2 and targets ubiquitin-mediated degradation, thereby negatively regulating the downstream cell protective activity of Nrf2 (31). In the present case, the mutation was a pipework mutation, which led to the mutation of the

amino acid at position 599 of the gene-encoded protein from serine to tryptophan and its termination at position 671, thus leading to cancerous cell transformation (32). KEAP1 mutations are common in both lung adenocarcinoma (~17%) and squamous cell carcinoma (10-12%) (33), although, to the best of our knowledge, there have been no reports of KEAP1 gene mutations in PEAC. Lung adenocarcinomas with co-mutated KEAP1 driver genes do not respond to immunotherapy despite a high tumor mutation load, which may be associated with a poorer prognosis in patients with PEAC, according to a study published in 2020 in Annals of Oncology (34).

Covariant KRAS/KEAP1 may cause conventional immunotherapy to be ineffective. A retrospective study has reported that patients with advanced lung adenocarcinoma treated with a programmed cell death 1 (ligand 1) inhibitor in the context of KRAS/KEAP1 frequently exhibit poor disease-free survival and OS (35).

Currently, the treatment plan for primary pulmonary intestinal adenocarcinoma is similar to that for other types of primary pulmonary adenocarcinoma. Based on clinical staging, a comprehensive treatment plan with surgery as the main treatment, supplemented by radiotherapy, chemotherapy and/or targeted therapy, is adopted, and classic thoracic surgical intervention is the preferred treatment method (5). It has been reported that after 2-3 weeks of treatment with pemetrexed, carboplatin and monoclonal antibody against pabolizumab, as well as pemetrexed, carboplatin and chemotherapy, the condition remained stable (5,36).

To the best of our knowledge, the present study was the first case report of PEAC with systemic multiple bone and lymphatic metastasis. At present, treatment guidelines for this rare type of cancer are lacking. Considering that mutations in drug-resistant genes are frequently found in PEAC and immunotherapy may not be able to effectively control the progression of cancer, it may be concluded that an effective alternative and personalized treatment is necessary.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL, SZ and WY conceived and designed the study, and wrote the manuscript. ZF and XW obtained MRI and CT images. PY, XL and YJ collected and analyzed the data. WJ performed the pathological examination and provided experimental support. SZ and WY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the case information and images to be published in this case report.

Competing interests

The authors declare that they have no competing interests.

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