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CASE REPORT

Diagnosis and treatment of primary pulmonary enteric adenocarcinoma: Report of Six cases

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Author contributions: Tu LF and Shen YH helped get all the data of the cases from hospital; Sheng LY, Tu LF, Zhou JY, Wang XF, Wang YH, and Shen Q drafted the manuscript; Shen YH is the supervisor; all authors read and approved the final manuscript.

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Abstract

BACKGROUND

Primary pulmonary enteric adenocarcinoma (PEAC) is a very rare subtype of invasive adenocarcinoma, and there have been no large studies on PEAC to date. Therefore, it is necessary to obtain much more information about the clinical and pathological features, diagnosis, differential diagnosis, and treatment of PEAC.

CASE SUMMARY

All clinical data of six patients with confirmed PEAC from 2013 to 2018 were collected, and data on diagnosis, differential diagnosis, and treatment of PEAC are discussed combined with all the associated literature. The mean age of six patients was 64.0 ± 5.6 (59-73) years old. Their clinical manifestations were heterogeneous, and during their disease course, there were no gastrointestinal symptoms. There was no evidence from colonoscopy or imaging studies to suggest digestive tract tumors or new metastases. The most commonly mutated gene was *KRAS* (50.0%), and the pathological features of the six cases were similar to those of colorectal cancer. CDX2 (83.3%) and CK7 (66.7%) had the highest positive rates upon immunohistochemical examination. In the associated literature, 252 cases were identified, and the most commonly mutated gene was *KRAS* (42.9%). Additionally, CDX2 (68.3%) and CK7 (85.8%) had the highest positive rates. Patients mainly received surgery, chemotherapy, and radiotherapy, immunotherapy was not included.

CONCLUSION

Positive results for CDX2 and CK7 play an important role in the diagnosis and differential diagnosis of PEAC, and immunotherapy or targeted therapy focused on *KRAS* needs to be further studied for the treatment of PEAC.

Key Words: Pulmonary enteric adenocarcinoma; Immunohistochemistry; Diagnosis; Treatment; KRAS; Case report

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Core Tip: Primary pulmonary enteric adenocarcinoma (PEAC) is a very rare subtype of invasive adenocarcinoma, and there have been no large studies on PEAC to date. All clinical data of six patients with confirmed PEAC from 2013 to 2018 were collected in this study, and data on the diagnosis, differential diagnosis, and treatment of PEAC are discussed combined with all the associated literature. Our findings highlight that positive results for CDX2 and CK7 play an important role in the diagnosis and differential diagnosis of PEAC, and immunotherapy or targeted therapy focused on *KRAS* needs to be further studied for the treatment of PEAC.

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INTRODUCTION

Primary pulmonary enteric adenocarcinoma (PEAC) is a very rare subtype of invasive adenocarcinoma. Its morphological and immunohistochemical findings are similar to those of colorectal cancer, but there is no evidence of any primary colorectal cancer[1].

Pulmonary enteric adenocarcinoma was first reported by Tsao and Fraser[2] in 1991. They reported a case of lung tumor with typical features of a differentiated intestinal epithelium, but after 4 years of follow-up, no primary tumors were found other than the lung tumor, which was considered to be a rare new subtype of pulmonary invasive adenocarcinoma, mainly seen in elderly patients[3].

The diagnosis of PEAC relies mainly on pathological and immunohistochemical results. When a primary pulmonary adenocarcinoma is mainly comprised of tissue with intestinal differentiation (> 50%), and the immunohistochemical results of the tumor cells are positive for at least one colorectal cancer-related immunohistochemical marker (CK20, CDX2, MUC2, villin, *etc.*), under the premise of the exclusion of gastrointestinal-derived tumors, the patient can finally be diagnosed with PEAC[4,5].

At present, reports related to PEAC are gradually increasing, especially studies on the diagnosis of PEAC and its differential diagnosis from lung metastases of colorectal cancer, but mostly these reports involve individual cases, and there are no large samples to date. Therefore, we collected six cases with PEAC diagnosed at the First Affiliated Hospital, Zhejiang University from 2013 to 2018 for retrospective analysis, and we analyzed the diagnosis, differential diagnosis, and treatment in combination with all associated literature to improve clinicians' understanding of this disease to identify more effective treatment.

CASE PRESENTATION

Chief complaints

All clinical data of six patients with confirmed PEAC from 2013 to 2018 were collected in this study. The ratio of males to females was 1:5, and their mean age was 64.0 ± 5.6 (59-73) years old. The chief complaints are shown in Table 1, including weakness of limb, cough, and so on.

History of present illness

None of the patients had a smoking history. The clinical manifestations were heterogeneous, and during the course of the disease, there were no gastrointestinal symptoms, such as melena, diarrhea, or abdominal pain. The clinical characteristics of six patients are shown in Table 1, including the location of lesion, metastasis, mass size, and tumor stage.

Table 1 Clinical features and chest computed tomography results of six patients with pulmonary enteric adenocarcinoma

Case	Gender	Age (yr)	Smoking history	Chief complaints	Lesion location	Mass size (cm)	Metastatic lymph node	Metastatic locations	Tumor stage	OS (mo)
1	Male	61	-	Weakness of left limb, numbness of left face	Posterior segment of RLL	3.6 × 2.8	Hilar and mediastinal	Intracranialregion	T2N2M1	Lost to follow-up
2	Female	73	-	A lung mass found by imaging studies with slightly cough	Posterior segment of LLL	2.8 × 1.5	-	-	T2N0M0	Lost to follow-up
3	Female	59	-	A lungmass found by imaging studies	LLL	1.3 × 0.6	-	-	T1N0M0	> 58
4	Female	64	-	Pain of right chest and back	RUL	2.1 × 2.0	Mediastinal	Right pleura	T1N2M1	Lost to follow-up
5	Female	59	-	Cough with fever	Bilateral	2.7 × 1.5	-	Intra-pulmonary	T4N0M1	> 9
6	Female	68	-	Cough,expect-ration, pain of left lower limb with difficult walking	RLL	6.7 × 5.4	Mediastinum	Intra-pulmonary + intracranialregion	T4N2M1	> 7

CT: Computed tomography; OS: Overall survival; RUL: Right upper lobe; RLL: Right lower lobe; LLL: Left lower lobe.

History of past illness

As listed in Table 1, case 1 had a history of tuberculosis and abdominal aortic stent implantation; case 2 suffered from hypertension, and she was allergic to iodine preparations. There was nothing apparent in the past history of case 3, and case 4 had a 10-year history of diabetes mellitus. Case 5 had been ill with hepatolithiasis for almost 40 years and progressed to liver cirrhosis for half a month, and she underwent cholecystectomy. Case 6 had a 20-year history of hypertension, diabetes mellitus, and protrusion of the lumbar intervertebral disc, and she had varicose exfoliation 10 years ago.

Personal and family history

In terms of personal and family history, there was nothing of note for case 5, and the other five patients' parents were all deceased for unknown reasons.

Physical examination

Case 2's breath sounds were rough, and case 4's were lower than normal. There was nothing wrong in any other aspects on the physical examination among six cases.

Laboratory examinations

All six patients had an abnormal increase in serum tumor markers (CEA, CA199, and CA125). The increase in CEA and CA199 was much more obvious than that of CA125, and the highest increase was 509 ng/mL and 1449.9 U/mL, respectively (Table 2). The other relevant serum tumor markers (neuron-specific enolase (NSE), serum cytokeratin 19 fragments (CYFRA21-1), *etc.*) were normal.

The immunohistochemistry examination mainly included specific antibodies against lung tumors and gastrointestinal tumors. The six cases were all tested for CDX2, CK7, and TTF-1. The positive rate of CDX2 was 83.3% (5/6), CK7 was 66.7% (4/6), and TTF-1 was 0 (Table 3).

In our study, four patients underwent genetic testing, and two had *KRAS* mutations (2/4, 50.0%); one had a *KRAS* missense mutation (20.11%), and the other had a *BRAC1* nonsense mutation (2.11%) and a *KRAS* missense mutation (47.22%). The tumor mutation burden of four cases was low or medium, and the average was 9.1 ± 3.5/Mb (Table 4).

Imaging examinations

There was no evidence to suggest digestive tract tumors in any patient on colonoscopy and imaging studies. The six patients all showed lung masses in different regions on chest computed tomography (Figure 1, Table 1), with a minimum of 1.3 cm × 0.6 cm and a maximum of 6.7 cm × 5.4 cm, two of which were associated with mediastinal

Table 2 Serum tumor markers of six patients with pulmonary enteric adenocarcinoma

Case	CEA (ng/mL)	CA199 (U/mL)	CA125 (U/mL)
1	33.5	40.8	33.5
2	2.4	5.8	7.4
3	1.7	2.6	9.3
4	509	132.6	217.8
5	2.7	243.6	13.7
6	1.1	1449.9	17

Table 3 Immunohistochemical results of six patients with pulmonary enteric adenocarcinoma

Case	CDX2	CK20	CK7	TTF-1	Napsin A	ALK-lung	Others
1	+	+	-	-	-	Not tested	Not tested
2	-	-	+	-	-	Not tested	SPA (-)
3	+	Not tested	-	-	Not tested	Not tested	CK19 (+), SPA (-)
4	+	+/-	+	-	-	-	p63 (-), CK5/6 (-), PAX8 (-)
5	+	Not tested	+	-	-	-	CD20 (-), MUC2 (-)
6	+	-	+	-	-	-	Ki-67 (low)

CDX2: Caudal type homeobox transcription factor 2; CK: Cytokeratin; TTF-1: Thyroid transcription factor-1; Napsin A: Novel aspartic proteinase of the pepsin family A; ALK: Anapastic lymphoma kinase; SPA: Staphylococal protein A; PAX8: Paired box gene 8; MUC2: Mucin 2; CD20: Cluster of differentiation 20; Ki-67: Antigen identified by monoclonal antibody Ki-67; p63: Protein 63.

Table 4 Genetic testing results of four patients with pulmonary enteric adenocarcinoma

Case	ALK	BRAF	BRCA1	BRCA2	EGFR	ERBB2	KRAS	ROS1	TMB (/Mb)
3	-	-	-	-	-	-	+	-	6.3
4	-	-	-	-	-	-	-	-	6.3
5	-	-	+	-	-	-	+	-	10.3
6	-	-	-	-	-	+	-	-	13.5

ALK: Anapastic lymphoma kinase; KRAS: V-Ki-ras2 Kirsten; BRAF: A gene that makes a protein called b-raf; BRCA: Breast cancer 1; EGFR: Epidermal growth factor receptor; ERBB2: V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; ROS1: C-ros oncogene 1 receptor kinase; TMB: Tumor mutation burden.

lymph node metastasis (Figure 1B).

Histopathology

All pathological findings were consistent with pulmonary adenocarcinoma, and there were more than 50% of tissues with intestinal differentiation in each specimen. Taking case 6 as an example, typically, the tumor tissue was arranged in an irregular large glandular tubular shape, and dusty necrosis and obvious nuclear fragmentation were visible in the glandular cavity. The cancer cells were highly columnar in shape and arranged in a pseudostratified layer, and the cytoplasm was red-stained. The brush border could also be seen under high magnification. The nucleus was deeply stained and arranged in a palisade (Figure 2).

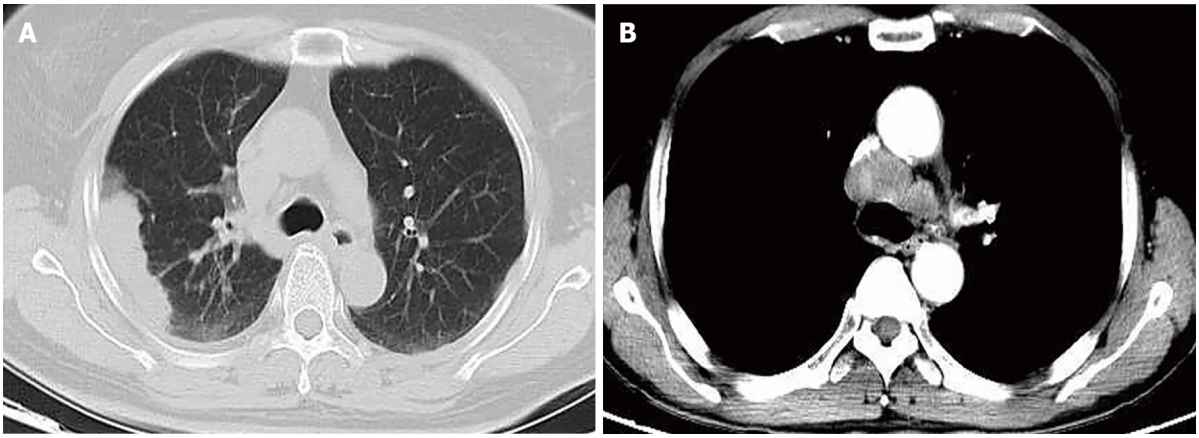

Figure 1 Chest computed tomography results of patients with primary pulmonary enteric adenocarcinoma. A: Case 4 with pulmonary enteric adenocarcinoma (PEAC) whose lesion was located in the right upper lobe; B: Case 1 with PEAC whose large lesion was located in the right lung, with mediastinal lymph node metastasis.

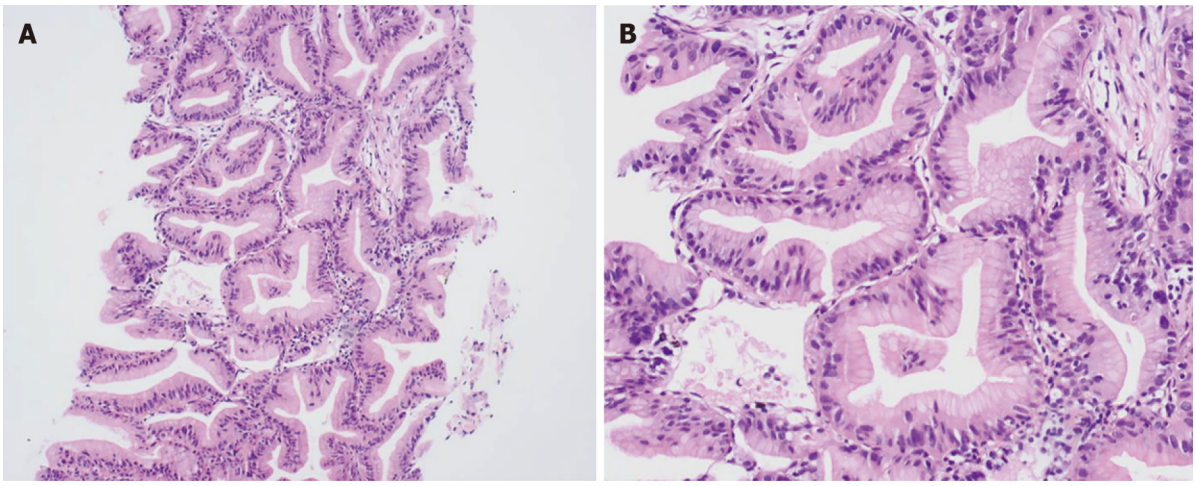

Figure 2 Pathology of case 6 with pulmonary enteric adenocarcinoma (HE staining). A: × 100; B: × 400.

FINAL DIAGNOSIS

Based on the above pathological and immunohistochemical results, the six patients were all diagnosed with PEAC with the exclusion of any gastrointestinal-derived primary tumors.

TREATMENT

Among the six patients, two did not undergo any treatment, and the others mainly received surgical resection, radiotherapy, systemic chemotherapy, and so on, and no patient was treated with immunotherapy or targeted therapy (Table 5).

OUTCOME AND FOLLOW-UP

The follow-up time of these patients was August 2019; three were lost to follow-up and the others were still alive. The longest overall survival (OS) was more than 58 mo, and the other two were 7 mo and 9 mo (Table 1). In addition, there was no evidence to suggest digestive tract tumors or any new metastases on colonoscopy and imaging studies at the end of follow-up.

Table 5 Treatment for six patients with pulmonary enteric adenocarcinoma

Case	Lesion location	Treatment
1	Posterior segment of RLL	Gamma knife for intracranial metastases, with 4 times of pemetrexed + cisplatin, 3 courses of ENDOSTAR, 30 times of radiotherapy, and tumor evaluation was PR; gamma knife again for new intracranial metastases on November 19, 2013
2	Posterior segment of LLL	No treatment
3	LLL	Surgical resection first, reoperation of the resection region because of relapse in September 2015, and no recurrence evidence
4	RUL	No treatment
5	Bilateral	TC chemotherapy and bevacizumab, tumor evaluation was SD
6	RLL	Gamma knife + chemotherapy (pemetrexed + carboplatin), tumor evaluation was SD

PR: Partial remission; TC: Paclitaxel-cisplatin; SD: Stable disease.

DISCUSSION

The six patients enrolled in this study were all diagnosed with PEAC. Classical pulmonary adenocarcinoma occurs in nonsmokers[6], especially women. These six patients had no smoking history, and five were female, suggesting that the characteristics of the populations with PEAC and classic pulmonary adenocarcinoma may be similar. In addition, the pathologic results of patients in this study were also consistent with the typical features of PEAC[7].

Common serum tumor markers for lung cancer include CEA, CYFRA 21-1, NSE, CA199, CA125, and so on[8], but their specificity is not high. Among them, CEA is not specific for most tumors, and CA199 is specifically expressed in digestive tract tumors (such as colorectal cancer and pancreatic cancer). CEA and CA199 have been used as tumor markers for colorectal cancer in Japan[9,10]. When CEA > 10 ng/mL and CA199 > 1000 U/mL, the probability of malignancy is high[11]. In this study, CEA and CA199 were significantly elevated in six patients (two with CEA > 10 ng/mL and one with CA199 > 100 U/mL), suggesting that PEAC may have some features in common with colorectal cancer in terms of serum tumor markers.

Because intestinal differentiated tissue accounts for the majority of PEAC, lung cancer markers (CK7, Napsin A, and TTF-1) and colorectal cancer markers (CK20, CDX2, villin, and MUC2) can be expressed simultaneously[12,13]. Previous studies have shown that almost all pulmonary adenocarcinomas express CK7, and most of them also express TTF-1, while MUC2 and CDX2 expression is low or absent. CK7 and CK20 are considered to be reliable markers that can identify PEAC and lung metastases of colorectal cancer[12,14]. With the analyses of these six patients and all the associated literature, CDX2 and CK7 had a higher positive rate on immunohistochemical staining than CK20 and TTF-1, so positive results for CDX2 and CK7 play an important role in the differential diagnosis of PEAC.

Specifically, one case showed no immunohistochemical markers related to colorectal cancer (only for the markers used here), and CK7 was not expressed in any pulmonary enteric adenocarcinomas. This does not seem to be consistent with the theoretical immuno-histochemical performance, but there are certain special types of pulmonary enteric adenocarcinoma, such as CK7 and/or CK20 negative cases[15,16]. These special types of pulmonary enteric adenocarcinoma suggest that it is necessary to expand the sample size for further research to optimize the diagnosis of PEAC.

The sample size of previous studies related to the genetic testing of PEAC is small, and there is no uniform conclusion. Nottegar *et al*[17] found that *KRAS* is the most common mutation in PEAC (> 60%), rarely affecting the *EGFR*, *BRAF*, and *ALK* genes. Another study by the same team also showed that *KRAS* is a common mutated gene expressed in PEAC, and *PIK3CA* mutations and *ALK* rearrangements could also be seen, while *NRAS* mutations were very rare[18]. Feng *et al*[19] found no correlation between the *EGFR* gene status and the median survival time in patients with PEAC. For colorectal cancer, *KRAS*, *PIK3CA*, *BRAF*, and *NRAS* are common mutated genes, among which *KRAS* is the most common, accounting for 40% of colorectal cancer patients, *PIK3CA* accounts for 15%, *BRAF* accounts for 5%, and *NRAS* accounts for 3% [20]. This study indicates that *KRAS* is the most common genetic mutation in colorectal cancer, and this result needs to be confirmed in future research.

Details of the previously reported studies associated with PEAC are shown in the Supplementary Material (which illustrates all cases of PEAC until August 2019). The number of cases was 252, and the average age in most cases (n = 107) was 63.9 ± 11.5 (24-88) years old. It is obvious that CK7 (169/197, 85.8%) and CDX2 (155/227, 68.3%) had higher positive rates than CK20 (100/219, 45.7%) and TTF-1 (76/207, 36.7%) in the immunohistochemical results. For genetic testing, the positive rates of *EGFR* and *KRAS* were 16.0% (27/169) and 42.9% (60/140), respectively, and there were also several cases with gene mutations of *ERBB2*, *TP53*, and so on, but the number of these cases was quite small.

In addition, it is necessary to consider the possible targeted therapy for PEAC, including the corresponding targets for lung cancer (ALK, EGFR, ROS1, *etc.*) and colorectal cancer (vascular endothelial growth factor, EGFR, *etc.*), and the possibility of immunotherapy should not be excluded, but the specific targeted therapy and immunotherapy for PEAC is still inconclusive. Based on the findings of this study, immunotherapy or targeted therapy focusing on *KARS* can be further studied as a treatment for PEAC.

CONCLUSION

Positive results of CDX2 and CK7 play an important role in the differential diagnosis of PEAC, and immunotherapy or targeted therapy of *KRAS* can be further explored for the treatment of PEAC. This study promotes an understanding of this rare type of lung adenocarcinoma and provides new ideas about its differential diagnosis and treatment, but a larger sample size of lung enteric adenocarcinoma needs additional study in the future to improve patient prognosis.

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