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Clinicopathologic characteristics and management of pulmonary enteric adenocarcinoma: an observational study

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Abstract

Objective To explore the clinicopathological characteristics of pulmonary enteric adenocarcinoma (PEAC) and its treatment and prognosis.

Methods Patients with pathologically confirmed PEAC treated at Xuanwu Hospital, Capital Medical University, between 2019 and 2023 were retrospectively identified. Patients with colorectal adenocarcinoma were excluded. Clinical manifestations, imaging findings, pathological findings, treatment regimens, and prognostic data were reviewed.

Results Eight patients (three male, five female) of median age 67.5 years (range 50–79) were included. The most common symptom was cough (62.5%), with some patients reporting shortness of breath and chest tightness. Chest CT revealed soft tis0sue masses in six cases, a ground-glass nodule in one case, and multiple nodules accompanied by pleural effusion in one case. Histological examination showed tall columnar tumor cells that formed glandular or sieve-like structures. Immunohistochemistry showed that all cases were CK7-positive, seven were CDX2-positive, five were CK20-positive, five were villin-positive, and three were positive for all four markers. Genetic testing showed epidermal growth factor receptor gene mutation positivity in one case and Kirsten rat sarcoma viral oncogene homolog gene mutation positivity in another. Three patients with stage I–II disease underwent surgery, three with stage IV disease received chemotherapy and immunotherapy, and one with stage II disease received targeted therapy. The follow-up data showed that the prognosis of PEAC was related to clinical stage and the treatment regimen, with the longest survival being 58 months.

Conclusions PEAC is a rare type of lung adenocarcinoma with clinicopathological features similar to those of colorectal adenocarcinoma. Chest CT often shows a large soft tissue shadow, which must be diagnosed by a combination of pathology and immunohistochemistry. Early diagnosis, multimodal treatment, and immunotherapy may prolong survival.

Keywords: pulmonary enteric adenocarcinoma, clinicopathological characteristics, diagnosis, treatment, prognosis

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Pulmonary enteric adenocarcinoma (PEAC) is a distinct variant of lung adenocarcinoma with a histological morphology resembling that of colorectal adenocarcinoma. First reported in 1991 [1], PEAC was recognized as an independent variant of primary invasive lung adenocarcinoma in the 2011 international multidisciplinary classification published by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society [2] and was formally included as a separate histological subtype in the 2015 World Health Organization classification [3]. PEAC is defined by the presence of >50% tumor cells showing enteric differentiation and expression of at least one intestinal lineage marker. As of 2020, fewer than 300 cases have been reported worldwide [4]. This study summarizes the clinicopathologic profile of PEAC and its management at our center.

Patients and Methods

Study population and ethics

Patients with pathologically confirmed PEAC managed at Xuanwu Hospital between 2019 and 2023 were retrospectively identified. The inclusion criteria were as follows: a histological diagnosis of PEAC; colorectal adenocarcinoma ruled out by systemic evaluation; and complete clinical, imaging, pathologic, and treatment data available. Patients with other systemic malignancies were excluded. The study was approved by our institutional ethics committee (approval number 197-002 [2024]). All patients provided informed consent.

Data collection and follow-up

Information on sex, age, major symptoms, imaging features, pathological and immunohistochemistry findings, molecular alterations, treatments, and outcomes was obtained from the inpatient and outpatient records. Response to treatment and survival were assessed by chart review. Follow-up ended in December 2023 or at the time of death, whichever came first.

Pathology review and ancillary testing

A respiratory physician with experience in lung cancer pathology and a pathologist jointly reviewed hematoxylin–eosin-stained sections to assess morphology, immunohistochemistry profiles, and molecular status. Immunohistochemistry was performed using the EnVision two-step method (antibodies/kits from Roche, Shanghai, China). *EGFR, ALK, ROS1*, and KRAS mutations were assessed by amplification refractory mutation system-based quantitative real-time polymerase chain reaction assays. Positive and negative controls were included for quality assurance.

Results

General characteristics

Eight patients (three male, five female) were treated for PEAC during the study period. The median age was 67.5 years (range 50–79). None had a family history of lung cancer and three had a history of smoking. The most common presentation was cough (n=5, 62.5%; one with hemoptysis) with one case each of wheeze and of chest pain with dyspnea as a result of massive pleural effusion. One patient was asymptomatic. Two patients had clinical stage I disease, two had stage II, and four had stage IV.

Imaging findings

The most common findings on chest CT were peripheral soft tissue masses with lobulation and pleural traction, with one lesion containing an air-filled cavity. One patient had a ground-glass nodule, and one had multiple pulmonary nodules accompanied by pleural effusion bilaterally. Staging with brain magnetic resonance imag-

Table 1. Clinicopathological characteristics, treatments, and outcomes in eight patients with pulmonary enteric adenocarcinoma.

No.	Sex	Age (y)	Symptoms	CT features	CK7	CK20	CDX2	Villin	TTF-1	Gene alteration	Treatment	Outcome	Survival (months)
1	Female	62	None	Left lower-lobe ground-glass nodule, 1.1 × 1.2 × 1.0 cm	+	—	—	—	—	NA	Left lower-lobe wedge resection + left mediastinal lymph-node dissection	Alive	58
2	Female	66	Wheezing	Left upper-lobe apicoposterior segment mass, 6.0 × 5.4 × 3.7 cm	+	—	—	—	—	—	Left upper lobectomy + mediastinal lymph-node dissection; 4 cycles adjuvant carboplatin + pemetrexed	Alive	53
3	Female	69	Cough	Left lower-lobe patchy high-density lesion with cavitation	+	—	—	—	—	—	Left lower-lobe wedge resection + left lymph-node dissection	Alive	45
4	Male	66	Cough	Right upper-lobe anterio r segment mass (~5.0 cm)	+	—	—	—	—	KRAS	Pemetrexed + carboplatin + PD-1 inhibitor induction; maintenance pemetrexed + PD-1; subsequent regimens after progression	Deceased	33
5	Female	50	Chest pain, dyspnea	Right lower-lobe basal segment mass (6.1 × 5.1 cm) with right pleural effusion	+	—	—	—	—	—	Pemetrexed + bevacizumab (1 cycle)	Deceased	2
6	Female	79	Shortness of breath	—	+	—	—	—	—	—	Carboplatin + pemetrexed + PD-1 inhibitor induction; maintenance pemetrexed + PD-1	Alive (progression-free survival 16 months)	—
7	Male	73	—	—	+	—	—	—	—	—	Carboplatin + pemetrexed + PD-1 inhibitor induction; maintenance pemetrexed + PD-1; later nab-paclitaxel + cisplatin, then gemcitabine; anlotinib	Deceased	33
8	Male	76	Cough, hemoptysis	Left lower-lobe mass (6.0 × 4.5 × 8.0 cm)	+	—	—	—	—	EGFR	Gefitinib (9 months) → furmonertinib (discontinued for GI AEs); best supportive care	Deceased	21

Notes: +, positive; −, negative (including some per-patient immunohistochemistry details that could not be unambiguously recovered from the source file).AEs, adverse effects; GI, gastrointestinal; NA, not assessed; PD-1, programmed cell death protein-1; TTF-1; thyroid transcription factor-1

ing, abdominal CT, neck ultrasonography, bone scintigraphy, and/or PET/CT revealed hilar/mediastinal lymph node metastases in four cases, cervical nodal metastasis in one, bilateral intrapulmonary metastases in two, and pleural metastasis with malignant effusion in two. No distant organ metastases were identified.

Pathology and immunohistochemistry

Specimens included three surgical resections, four percutaneous lung biopsies, and one transbronchial cryobiopsy. Histologically, tall columnar tumor cells formed glandular or cribriform structures with coarse chromatin, readily identifiable mitoses, and frequent geographic necrosis, distinct from typical lung adenocarcinoma; two cases also contained conventional adenocarcinoma with micropapillary foci. Immunohistochemistry showed CK7 positivity in all cases, CDX2 positivity in seven, CK20 positivity in five, and villin positivity in five. Three patients expressed all four markers. Four cases were positive for thyroid transcription factor-1 (two focally). Immunohistochemistry for PD-L1 was performed in four patients, with one showing >50% expression and three being negative.

Molecular alterations

One case harbored an *EGFR* mutation and another a *KRAS* mutation. All tested cases were negative for *ALK* and *ROS1*.

Treatment and outcomes

Three patients underwent surgery. Two patients underwent surgery alone for stage I disease and remain long-term survivors. One with stage II disease received four cycles of adjuvant carboplatin + pemetrexed and is alive at the last follow-up (longest observed survival, 58 months). One patient with stage II disease and an *EGFR* mutation declined surgery. In this case, gefitinib controlled the disease for nine months before progression. Without resistance testing, treatment was switched to furmonertinib, which was discontinued because of gastrointestinal adverse effects, and the patient died 21 months after diagnosis. Two of four patients with stage IV disease received first-line carboplatin + pemetrexed + a PD-1 inhibitor, achieved a partial response after two cycles, and continued pemetrexed + the PD-1 inhibitor as maintenance therapy. One of these patients had remained progression-free for 16 months at the last follow-up; the other progressed at 18 months, failed subsequent nab-paclitaxel + cisplatin and then gemcitabine monotherapy, received anlotinib with limited benefit, and died 33 months after diagnosis. One patient with rapidly accumulating pleural effusion and poor performance status received one cycle of pemetrexed + bevacizumab, which was complicated by persistent effusion, pulmonary infection, and heart failure, and died two months after diagnosis. One patient with multiple comorbidities received traditional Chinese medicine only and died 10 months after diagnosis.

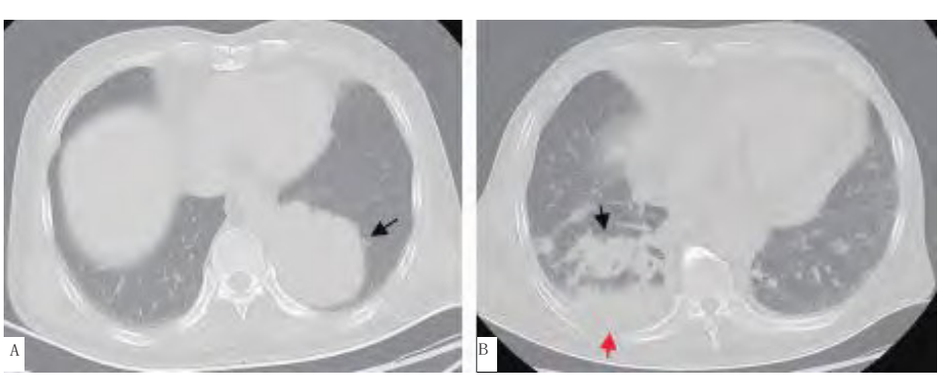


Figure 1. Manifestations of pulmonary enteric adenocarcinoma on chest CT. (A) Mass-like soft tissue lesion in the left lower lung (black arrow). (B) Nodules (black arrow) with pleural effusion (red arrow).

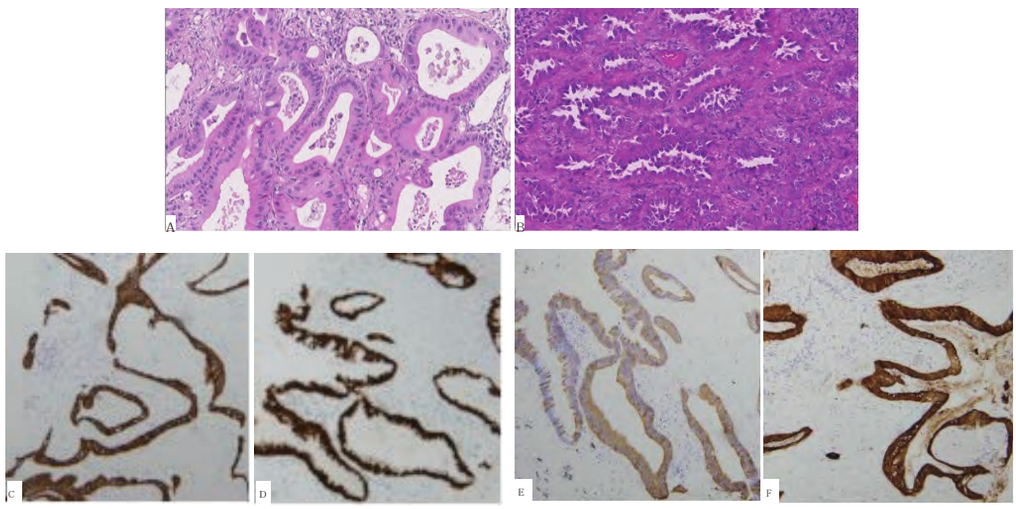


Figure 2. Representative histopathological findings in pulmonary enteric adenocarcinoma (×200) and results of immunohistochemistry (×100). (A) H&E staining of pulmonary enteric adenocarcinoma. (B) H&E staining of conventional lung adenocarcinoma. (C) CK7-positive. (D) CDX2-positive. (E) CK20-positive. (F) Villin-positive. H&E, hematoxylin–eosin.

Discussion

PEAC has been recognized as a rare histological subtype of lung adenocarcinoma for more than a decade and accounts for about 0.6% of lung adenocarcinomas [5]. Although its pathogenesis remains incompletely understood, shared stem cell populations within the mucosa of the lower respiratory and gastrointestinal tracts may help to explain the striking histological similarity between PEAC and colorectal carcinoma [6].

Clinical characteristics

Women constituted the majority of our cohort of eight patients, and the median age at diagnosis tended to be older, as previously reported [7]. However, other studies have noted that the proportion of men is higher for PEAC than for invasive lung adenocarcinoma (76% vs. 50%) [8], which may reflect the limited number of published reports on PEAC and heterogeneity across studies. In our series, the most common presenting symptom was cough, followed by chest pain, dyspnea, and wheeze. Early-stage patients were often asymptomatic. Overall, the clinical presentation did not differ markedly from that of invasive lung adenocarcinoma [8,9].

Imaging characteristics

Chest CT typically shows peripheral lesions, usually >3 cm in diameter, which most often appear as solid nodules or masses [4]. PEAC lesions tend to be larger than invasive lung adenocarcinoma and rarely present as pure ground-glass or part-solid nodules [4,8,10]. In one of our cases, PEAC manifested as a ground-glass nodule, indicating that PEAC can present with a ground-glass appearance, albeit not commonly. PEAC frequently shows early metastatic spread, and CT often reveals enlarged hilar or mediastinal lymph nodes. Distant metastases may involve the liver, bone, and skin, with occasional pancreatic involvement. Although invasive lung adenocarcinoma can also metastasize, it generally progresses more slowly than PEAC [10]. One of the patients in this series presented with multiple nodules and a large pleural effusion in the right lung without a dominant primary mass, underscoring the propensity of PEAC for both intrapulmonary and extrathoracic dissemination and the challenge of differentiating it from pulmonary metastases of colorectal adenocarcinoma. Nevertheless, gastro-

intestinal endoscopy and PET/CT revealed no evidence of a colorectal primary, supporting a diagnosis of PEAC.

Pathological characteristics of PEAC

The diagnostic criteria for PEAC require >50% enteric differentiation together with expression of at least one intestinal differentiation marker by immunohistochemistry. However, most tumors are a mixture of histological subtypes, with purely enteric morphology being present in only 17.4% of cases [11]. In our series, two cases showed micropapillary components, while the remaining six were purely enteric on available specimens. Given that a substantial proportion of our samples were from needle biopsies, undersampling cannot be excluded and may have limited assessment of all histological components. Beyond lung lineage markers, PEAC typically expresses at least one marker of colorectal adenocarcinoma. In this cohort, all cases were positive for CK7, 87.5% were positive for CK20, and 62.5% were positive for villin, while 50% of cases showed partial expression of thyroid transcription factor-1, which is in line with previous studies [12,13]. Combined testing for CK7 and CDX2 has been proposed as a reliable immunophenotypic signature for a diagnosis of PEAC, even for small biopsies and cytology specimens, and helps to distinguish PEAC from invasive lung adenocarcinoma and metastatic colorectal carcinoma [11,14]. When differentiation is difficult, surfactant protein A, thyroid transcription factor-1, and napsin A can serve as adjunctive markers [11]. Notably, the CK7+/CDX2+ profile offers relatively high sensitivity (71.3%) and specificity (82%) for discriminating PEAC from colorectal carcinoma [14]. Although villin is frequently positive and is an important marker in PEAC [4,15], its brush-border expression pattern mirrors that of colorectal carcinoma, limiting its value for distinguishing PEAC from colorectal pulmonary metastases. In our cohort, four patients underwent PD-L1 immunohistochemistry; three were negative and one showed >50% expression, suggesting that immunotherapy may benefit a subset of patients.

Genomic alterations

Among our eight patients, one harbored an *EGFR* mutation and one a *KRAS* mutation, while *ALK* and *ROS1* were negative in all tested cases. Previous studies indicate that *EGFR* mutation rates are lower in PEAC than in invasive lung adenocarcinoma [4,8]. Reported *KRAS* mutation frequencies vary, with most series suggesting that the *KRAS* mutation rate is higher in PEAC than in conventional lung adenocarcinoma but lower than in metastases of colorectal carcinoma [4,8,11]. Conversely, some reports have described tumors that are wild type for both *EGFR* and *KRAS* [9].

Treatment and prognosis

At present, no dedicated guidelines or consensus statements specifically address PEAC. Most reported cases have been managed according to the principles used for lung adenocarcinoma: surgical resection is preferred for stage I–IIIA disease, whereas stage IIIB–IV disease is usually treated with systemic therapy centered on chemotherapy. Considering that effective *KRAS*-targeted agents have historically been limited and *EGFR* mutations are uncommon, opportunities for targeted therapy are fewer than for other subtypes of lung adenocarcinoma. Some studies have suggested that taxane–platinum regimens, which have activity in both colorectal and lung adenocarcinoma, may be particularly effective [16,17]. In our cohort, two patients with stage IV disease received first-line pemetrexed + a platinum agent + a PD-1 inhibitor; their progression-free survival (PFS) was not shorter than that typically observed in invasive lung adenocarcinoma, providing evidence to support use of pemetrexed + a platinum agent as a reasonable first-line option for PEAC. Evidence for immunotherapy in PEAC remains limited. In our series, the two patients who received chemotherapy also re-

ceived immunotherapy. One progressed after 18 months of maintenance therapy, while the other remains stable at 16 months, a PFS that is notably longer than the median achieved with pemetrexed maintenance monotherapy in non-small-cell lung cancer [18,19]. Similar to trends in invasive lung adenocarcinoma, these observations suggest that adding immunotherapy to chemotherapy may prolong PFS beyond that achievable by chemotherapy alone. However, larger clinical studies are needed to substantiate this conclusion.

As a rare subtype of lung adenocarcinoma, PEAC has not been well characterized in terms of its prognosis. One study reported that overall outcomes may be better in patients with PEAC than in those with conventional lung adenocarcinoma [20]. Our experience has been that patients with earlier-stage disease who undergo complete curative resection have favorable outcomes. In cases with stage IV disease, the prognosis appears to correlate with receiving chemotherapy and its effectiveness, which is consistent with a previous report [17]. Two of our three patients who received chemotherapy derived substantial benefit, while the remaining patient experienced rapid progression that was ultimately fatal, highlighting the biological heterogeneity of PEAC and the need for further research to define phenotypes and optimize selection of therapy.

Conclusion

PEAC is a rare subtype of lung adenocarcinoma with nonspecific demographic and clinical features. Chest CT often shows a large soft tissue mass, and definitive diagnosis requires integration of histopathology and immunohistochemistry. Early detection, multimodal therapy, and judicious use of immunotherapy may help to extend survival.

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Author contributions

Yu Chen contributed to the study conception, literature review, and drafting of the manuscript. Yajie Wang was responsible for data collection, analysis, and interpretation. Xiuhong Nie supervised the study, provided critical revisions, and is the corresponding author. All authors read and approved the final manuscript.

Conflicts of Interest

All authors declare no conflicts of interest.

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