

World Journal of *Clinical Cases*

World J Clin Cases 2021 October 26; 9(30): 8953-9319



REVIEW

- 8953 Endothelial progenitor cells and coronary artery disease: Current concepts and future research directions
Xiao ST, Kuang CY

MINIREVIEWS

- 8967 Regulation of bone metabolism mediated by β -adrenergic receptor and its clinical application
Zhong XP, Xia WF
- 8974 Tricuspid valve endocarditis: Cardiovascular imaging evaluation and management
Fava AM, Xu B

ORIGINAL ARTICLE**Case Control Study**

- 8985 Novel application of multispectral refraction topography in the observation of myopic control effect by orthokeratology lens in adolescents
Ni NJ, Ma FY, Wu XM, Liu X, Zhang HY, Yu YF, Guo MC, Zhu SY

Retrospective Cohort Study

- 8999 Uncertainty in illness and coping styles: Moderating and mediating effects of resilience in stroke patients
Han ZT, Zhang HM, Wang YM, Zhu SS, Wang DY

Retrospective Study

- 9011 Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus
Zhang DY, Huang GR, Ku JW, Zhao XK, Song X, Xu RH, Han WL, Zhou FY, Wang R, Wei MX, Wang LD
- 9023 Preliminary establishment of a spinal stability scoring system for multiple myeloma
Yao XC, Shi XJ, Xu ZY, Tan J, Wei YZ, Qi L, Zhou ZH, Du XR
- 9038 Effect of intrauterine perfusion of granular leukocyte-colony stimulating factor on the outcome of frozen embryo transfer
Zhu YC, Sun YX, Shen XY, Jiang Y, Liu JY
- 9050 "An integrated system, three separated responsibilities", a new fever clinic management model, in prevention and control of novel coronavirus pneumonia
Shen J, He Q, Shen T, Wu ZQ, Tan MM, Chen YL, Weng Q, Nie LM, Zhang HF, Zheng B, Zhang J

Clinical Trials Study

- 9059** Single dose dexamethasone prophylaxis of postembolisation syndrome after chemoembolisation in hepatocellular carcinoma patient: A randomised, double-blind, placebo-controlled study
Sainamthip P, Kongphanich C, Prasongsook N, Chirapongsathorn S

Observational Study

- 9070** Serum calcium, albumin, globulin and matrix metalloproteinase-9 levels in acute cerebral infarction patients
Zhong TT, Wang G, Wang XQ, Kong WD, Li XY, Xue Q, Zou YA

SYSTEMATIC REVIEWS

- 9077** Neoadjuvant radiotherapy dose escalation for locally advanced rectal cancers in the new era of radiotherapy: A review of literature
Delishaj D, Fumagalli IC, Ursino S, Cristaudo A, Colangelo F, Stefanelli A, Alghisi A, De Nobili G, D'Amico R, Cocchi A, Ardizzoia A, Soatti CP

META-ANALYSIS

- 9090** Clinical significance of breast cancer susceptibility gene 1 expression in resected non-small cell lung cancer: A meta-analysis
Gao Y, Luo XD, Yang XL, Tu D

CASE REPORT

- 9101** Particular tumor of the pancreas: A case report
Zhu MH, Nie CF
- 9108** Dynamic changes in the radiologic manifestation of a recurrent checkpoint inhibitor related pneumonitis in a non-small cell lung cancer patient: A case report
Tan PX, Huang W, Liu PP, Pan Y, Cui YH
- 9114** Spontaneous rupture of a mucinous cystic neoplasm of the liver resulting in a huge biloma in a pregnant woman: A case report
Kośnik A, Stadnik A, Szczepankiewicz B, Patkowski W, Wójcicki M
- 9122** Diagnosis and laparoscopic excision of accessory cavitated uterine mass in a young woman: A case report
Hu YL, Wang A, Chen J
- 9129** Unusual cervical foreign body - a neglected thermometer for 5 years: A case report
Yang L, Li W
- 9134** Long-term survival of a patient with pancreatic cancer and lung metastasis: A case report and review of literature
Yang WW, Yang L, Lu HZ, Sun YK
- 9144** Synchronous diagnosis and treatment of acute myeloid leukemia and chronic lymphocytic leukemia: Two case reports
Chen RR, Zhu LX, Wang LL, Li XY, Sun JN, Xie MX, Zhu JJ, Zhou D, Li JH, Huang X, Xie WZ, Ye XJ

- 9151** Conversion therapy of hepatic artery ligation combined with transcatheter arterial chemoembolization for treating liver cancer: A case report
Feng GY, Cheng Y, Xiong X, Shi ZR
- 9159** Hemophagocytic lymphohistiocytosis secondary to composite lymphoma: Two case reports
Shen J, Wang JS, Xie JL, Nong L, Chen JN, Wang Z
- 9168** Fatal visceral disseminated varicella-zoster virus infection in a renal transplant recipient: A case report
Wang D, Wang JQ, Tao XG
- 9174** Choriocarcinoma misdiagnosed as cerebral hemangioma: A case report
Huang HQ, Gong FM, Yin RT, Lin XJ
- 9182** Rapid progression of colonic mucinous adenocarcinoma with immunosuppressive condition: A case report and review of literature
Koseki Y, Kamimura K, Tanaka Y, Ohkoshi-Yamada M, Zhou Q, Matsumoto Y, Mizusawa T, Sato H, Sakamaki A, Umezu H, Yokoyama J, Terai S
- 9192** Temporary pacemaker protected transjugular intrahepatic portosystemic shunt in a patient with acute variceal bleeding and bradyarrhythmia: A case report
Yao X, Li SH, Fu LR, Tang SH, Qin JP
- 9198** Recurrent pyogenic liver abscess after pancreatoduodenectomy caused by common hepatic artery injury: A case report
Xie F, Wang J, Yang Q
- 9205** Transient ventricular arrhythmia as a rare cause of dizziness during exercise: A case report
Gao LL, Wu CH
- 9211** Successful management of infected right iliac pseudoaneurysm caused by penetration of migrated inferior vena cava filter: A case report
Weng CX, Wang SM, Wang TH, Zhao JC, Yuan D
- 9218** Anterior abdominal abscess - a rare manifestation of severe acute pancreatitis: A case report
Jia YC, Ding YX, Mei WT, Xue ZG, Zheng Z, Qu YX, Li J, Cao F, Li F
- 9228** Monteggia type-I equivalent fracture in a fourteen-month-old child: A case report
Li ML, Zhou WZ, Li LY, Li QW
- 9236** Diagnosis and treatment of primary pulmonary enteric adenocarcinoma: Report of Six cases
Tu LF, Sheng LY, Zhou JY, Wang XF, Wang YH, Shen Q, Shen YH
- 9244** Choroidal metastatic mucinous abscess caused by *Pseudomonas aeruginosa*: A case report
Li Z, Gao W, Tian YM, Xiao Y
- 9255** Diagnosis and treatment of acute graft-versus-host disease after liver transplantation: Report of six cases
Tian M, Lyu Y, Wang B, Liu C, Yu L, Shi JH, Liu XM, Zhang XG, Guo K, Li Y, Hu LS

- 9269** Hepatic portal venous gas without definite clinical manifestations of necrotizing enterocolitis in a 3-day-old full-term neonate: A case report
Yuan K, Chen QQ, Zhu YL, Luo F
- 9276** Emergence of lesions outside of the basal ganglia and irreversible damage to the basal ganglia with severe β -ketothiolase deficiency: A case report
Guo J, Ren D, Guo ZJ, Yu J, Liu F, Zhao RX, Wang Y
- 9285** Skeletal muscle metastasis with bone metaplasia from colon cancer: A case report and review of the literature
Guo Y, Wang S, Zhao ZY, Li JN, Shang A, Li DL, Wang M
- 9295** Biopsy-confirmed fenofibrate-induced severe jaundice: A case report
Lee HY, Lee AR, Yoo JJ, Chin S, Kim SG, Kim YS
- 9302** Missense mutation in *DYNC1H1* gene caused psychomotor developmental delay and muscle weakness: A case report
Ding FJ, Lyu GZ, Zhang VW, Jin H
- 9310** Isolated hepatic tuberculosis associated with portal vein thrombosis and hepatitis B virus coinfection: A case report and review of the literature
Zheng SM, Lin N, Tang SH, Yang JY, Wang HQ, Luo SL, Zhang Y, Mu D

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Rahul Gupta, MBBS, MCh, MD, Assistant Professor, Chief Doctor, Consultant Physician-Scientist, Surgeon, Department of Gastrointestinal Surgery, Synergy Institute of Medical Sciences, Dehradun 248001, Uttarakhand, India. rahul.g.85@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Lin*, Production Department Director: *Yin-Jie Ma*, Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

October 26, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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

Ling-Fang Tu, Ling-Yan Sheng, Jian-Ying Zhou, Xue-Fen Wang, Yue-Hong Wang, Qian Shen, Yi-Hong Shen

ORCID number: Ling-Fang Tu 0000-0003-4348-6592; Ling-Yan Sheng 0000-0003-2491-3675; Jian-Ying Zhou 0000-0002-8924-935X; Xue-Fen Wang 0000-0002-3953-7388; Yue-Hong Wang 0000-0002-0719-3197; Qian Shen 0000-0001-5820-6034; Yi-Hong Shen 0000-0002-7815-9973.

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.

Supported by Medicine and Health Project of Zhejiang Province, China, No. 2018KY049.

Informed consent statement: Informed consent was obtained from the patients for publication of this report and accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest for this manuscript.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an

Ling-Fang Tu, Ling-Yan Sheng, Jian-Ying Zhou, Xue-Fen Wang, Yue-Hong Wang, Qian Shen, Yi-Hong Shen, Department of Respiratory Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Corresponding author: Yi-Hong Shen, MD, Chief Doctor, Department of Respiratory Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. drsyh@zju.edu.cn

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

open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 21, 2021

Peer-review started: May 21, 2021

First decision: June 15, 2021

Revised: June 28, 2021

Accepted: August 20, 2021

Article in press: August 20, 2021

Published online: October 26, 2021

P-Reviewer: Chen SY

S-Editor: Ma YJ

L-Editor: Wang TQ

P-Editor: Wu RR



©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Tu LF, Sheng LY, Zhou JY, Wang XF, Wang YH, Shen Q, Shen YH. Diagnosis and treatment of primary pulmonary enteric adenocarcinoma: Report of Six cases. *World J Clin Cases* 2021; 9(30): 9236-9243

URL: <https://www.wjgnet.com/2307-8960/full/v9/i30/9236.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i30.9236>

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	Intracranial region	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 lung mass 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, expectoration, pain of left lower limb with difficult walking	RLL	6.7 × 5.4	Mediastinum	Intra-pulmonary + intracranial region	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: Anaplastic lymphoma kinase; SPA: Staphylococcal 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: Anaplastic 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).

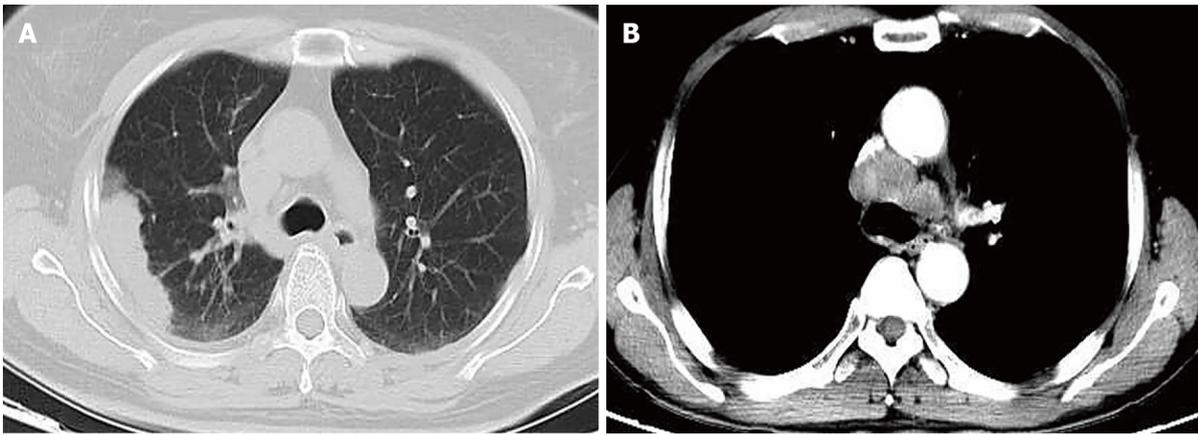


Figure 1 Chest computed tomography results of patients with primary pulmonary enteric adenocarcinoma. A: Case 4 with pulmonary enteric adenocarcinoma (PEAC) whose lesion was located in the right upper lobe; B: Case 1 with PEAC whose large lesion was located in the right lung, with mediastinal lymph node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

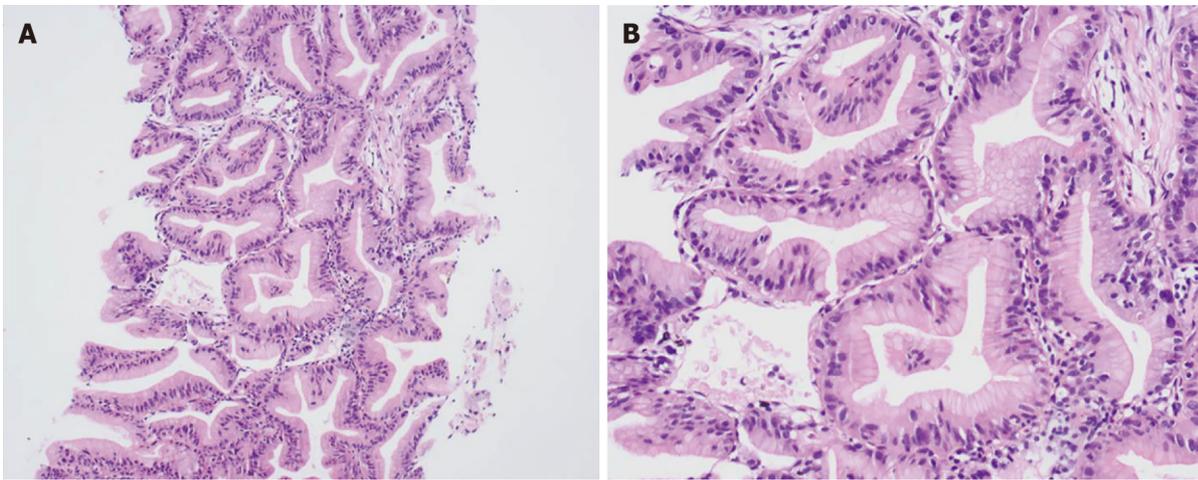


Figure 2 Pathology of case 6 with pulmonary enteric adenocarcinoma (HE staining). A: $\times 100$; B: $\times 400$.

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.

REFERENCES

- 1 **Lin LI**, Xu CW, Zhang BO, Liu RR, Ge FJ, Zhao CH, Jia RU, Qin QH, Stojic J, Wang Y, Xu JM. Clinicopathological observation of primary lung enteric adenocarcinoma and its response to chemotherapy: A case report and review of the literature. *Exp Ther Med* 2016; **11**: 201-207 [PMID: 26889240 DOI: 10.3892/etm.2015.2864]
- 2 **Tsao MS**, Fraser RS. Primary pulmonary adenocarcinoma with enteric differentiation. *Cancer* 1991; **68**: 1754-1757 [PMID: 1913519 DOI: 10.1002/1097-0142(19911015)68:8<1754::aid-cnrcr2820680818>3.0.co;2-e]
- 3 **Ou SH**, Kawaguchi T, Soo RA, Kitaichi M. Rare subtypes of adenocarcinoma of the lung. *Expert Rev Anticancer Ther* 2011; **11**: 1535-1542 [PMID: 21999127 DOI: 10.1586/era.11.99]
- 4 **László T**, Lacza A, Tóth D, Molnár TF, Kálmán E. Pulmonary enteric adenocarcinoma indistinguishable morphologically and immunohistologically from metastatic colorectal carcinoma. *Histopathology* 2014; **65**: 283-287 [PMID: 24571601 DOI: 10.1111/his.12403]
- 5 **Wang CX**, Liu B, Wang YF, Zhang RS, Yu B, Lu ZF, Shi QL, Zhou XJ. Pulmonary enteric adenocarcinoma: a study of the clinicopathologic and molecular status of nine cases. *Int J Clin Exp Pathol* 2014; **7**: 1266-1274 [PMID: 24696747]
- 6 **Yin Z**, Zhou B, He Q, Li M, Guan P, Li X, Cui Z, Xue X, Su M, Ma R, Bai W, Xia S, Jiang Y, Xu S, Lv Y. Association between polymorphisms in DNA repair genes and survival of non-smoking female patients with lung adenocarcinoma. *BMC Cancer* 2009; **9**: 439 [PMID: 20003463 DOI: 10.1186/1471-2407-9-439]
- 7 **Matsushima J**, Yazawa T, Suzuki M, Takahashi Y, Ota S, Nakajima T, Yoshino I, Yokose T, Inoue T, Kawahara K, Nakatani Y. Clinicopathological, immunohistochemical, and mutational analyses of pulmonary enteric adenocarcinoma: usefulness of SATB2 and β -catenin immunostaining for differentiation from metastatic colorectal carcinoma. *Hum Pathol* 2017; **64**: 179-185 [PMID: 28438615 DOI: 10.1016/j.humpath.2017.04.006]
- 8 **Sato Y**, Fujimoto D, Uehara K, Shimizu R, Ito J, Kogo M, Teraoka S, Kato R, Nagata K, Nakagawa A, Otsuka K, Hamakawa H, Takahashi Y, Imai Y, Tomii K. The prognostic value of serum CA 19-9 for patients with advanced lung adenocarcinoma. *BMC Cancer* 2016; **16**: 890 [PMID: 27842505 DOI: 10.1186/s12885-016-2897-6]
- 9 **Chen M**, Liu P, Yan F, Xu S, Jiang Q, Pan J, He M, Shen P. Distinctive features of immunostaining and mutational load in primary pulmonary enteric adenocarcinoma: implications for differential diagnosis and immunotherapy. *J Transl Med* 2018; **16**: 81 [PMID: 29587865 DOI: 10.1186/s12967-018-1449-z]
- 10 **Kazama S**, Watanabe T. [Diagnosis of colorectal cancer by measurement of tumor markers]. *Nihon Rinsho* 2014; **72**: 71-76 [PMID: 24597351]
- 11 **Perkins GL**, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. *Am Fam Physician* 2003; **68**: 1075-1082 [PMID: 14524394]

- 12 **Yousem SA.** Pulmonary intestinal-type adenocarcinoma does not show enteric differentiation by immunohistochemical study. *Mod Pathol* 2005; **18**: 816-821 [PMID: 15605076 DOI: 10.1038/modpathol.3800358]
- 13 **Zhao L,** Huang S, Liu J, Zhao J, Li Q, Wang HQ. Clinicopathological, radiographic, and oncogenic features of primary pulmonary enteric adenocarcinoma in comparison with invasive adenocarcinoma in resection specimens. *Medicine (Baltimore)* 2017; **96**: e8153 [PMID: 28953659 DOI: 10.1097/MD.00000000000008153]
- 14 **Inamura K,** Satoh Y, Okumura S, Nakagawa K, Tsuchiya E, Fukayama M, Ishikawa Y. Pulmonary adenocarcinomas with enteric differentiation: histologic and immunohistochemical characteristics compared with metastatic colorectal cancers and usual pulmonary adenocarcinomas. *Am J Surg Pathol* 2005; **29**: 660-665 [PMID: 15832091 DOI: 10.1097/01.pas.0000160438.00652.8b]
- 15 **Hatanaka K,** Tsuta K, Watanabe K, Sugino K, Uekusa T. Primary pulmonary adenocarcinoma with enteric differentiation resembling metastatic colorectal carcinoma: a report of the second case negative for cytokeratin 7. *Pathol Res Pract* 2011; **207**: 188-191 [PMID: 20727680 DOI: 10.1016/j.prp.2010.07.005]
- 16 **Miyaoka M,** Hatanaka K, Iwazaki M, Nakamura N. CK7/CK20 Double-Negative Pulmonary Enteric Adenocarcinoma With Histopathological Evaluation of Transformation Zone Between Enteric Adenocarcinoma and Conventional Pulmonary Adenocarcinoma. *Int J Surg Pathol* 2018; **26**: 464-468 [PMID: 29411669 DOI: 10.1177/1066896918756737]
- 17 **Handa Y,** Kai Y, Ikeda T, Mukaida H, Egawa H, Kaneko M. Pulmonary enteric adenocarcinoma. *Gen Thorac Cardiovasc Surg* 2016; **64**: 749-751 [PMID: 26139021 DOI: 10.1007/s11748-015-0569-0]
- 18 **Nottegar A,** Tabbò F, Luchini C, Guerrera F, Gaudiano M, Bria E, Brunelli M, Chilosi M, Inghirami G. Pulmonary adenocarcinoma with enteric differentiation: Dissecting oncogenic genes alterations with DNA sequencing and FISH analysis. *Exp Mol Pathol* 2017; **102**: 276-279 [PMID: 28237660 DOI: 10.1016/j.yexmp.2017.02.014]
- 19 **Feng C,** Feng M, Gao Y, Zhao X, Peng C, Yang X, Zhang J. Clinicopathologic Significance of Intestinal-type Molecules' Expression and Different EGFR Gene Status in Pulmonary Adenocarcinoma. *Appl Immunohistochem Mol Morphol* 2019; **27**: 364-372 [PMID: 29489510 DOI: 10.1097/PAI.0000000000000632]
- 20 **De Roock W,** Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilias G, Kalogeras KT, Kotoula V, Papamichael D, Laurent-Puig P, Penault-Llorca F, Rougier P, Vincenzi B, Santini D, Tonini G, Cappuzzo F, Frattini M, Molinari F, Saletti P, De Dosso S, Martini M, Bardelli A, Siena S, Sartore-Bianchi A, Tabernero J, Macarulla T, Di Fiore F, Gangloff AO, Ciardiello F, Pfeiffer P, Qvortrup C, Hansen TP, Van Cutsem E, Piessevaux H, Lambrechts D, Delorenzi M, Tejpar S. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; **11**: 753-762 [PMID: 20619739 DOI: 10.1016/S1470-2045(10)70130-3]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

