Clinical Case Report

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Primary pulmonary hepatoid adenocarcinoma

A case report and review of the literature

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Abstract

Rationale: Hepatoid adenocarcinoma of lung (HAL) is a rare malignant tumor, which can be defined as a primary alpha-fetoprotein (AFP)-producing lung carcinoma. The majority of hepatoid adenocarcinoma (HAC) expressed AFP in tumor cells, but AFP expression is not required for its diagnosis according to the modified diagnostic criteria. Despite that HAC exhibits a poor prognosis and ineffective treatment options, early diagnosis and aggressive treatment can result in long-term survival.

Patient concerns: We report a 70-year-old Chinese male patient with alcoholic intake over 30 years and smoking history of 60 cigarettes per day for 40 years. He sought medical consultation for productive cough and hemoptysis sputum.

Diagnoses and interventions: Chest CT scan revealed a mass (6.4 × 5.5 cm) in the left lower lobe of the lung. The patient underwent curative surgical resection, and subsequently diagnosed as HAL.

Outcomes: Eighteen months after primary diagnosis, the patient died of multiple organ failure caused by distant metastases.

Lessons: Familiarizing with the clinical features and modified diagnostic criteria of this rare tumor may increase awareness of the disease among clinicians and pathologists, thereby avoiding misdiagnosis and mistreatment.

Abbreviations: AFP = α-fetoprotein, CEA = carcinoembryonic antigen, HAC = hepatoid adenocarcinoma, HAL = hepatoid adenocarcinoma of lung, HCC = hepatocellular carcinoma, IMRT = intensity-modulated radiation therapy, WBRT = Whole-brain radiation therapy, XRT = X-ray radiotherapy.

Keywords: α-fetoprotein, clinical feature, diagnostic criteria, hepatoid adenocarcinoma, immunohistochemistry, lung

1. Introduction

Hepatoid adenocarcinoma (HAC) is a rare α-fetoprotein (AFP)-producing tumor, which has a poor prognosis and ineffective treatment options. HAC consists of eosinophilic cytoplasm and centrally located nuclei that closely resembling the hepatocellular carcinoma (HCC) cells.[1] The primary sites of origin for HAC are lungs, with an occurrence rate of 5% among lung cancer cases.[2] Despite that conventional lung cancer treatments have been proven ineffective for treating hepatoid adenocarcinoma of lung (HAL), early diagnosis and aggressive treatment can result in long-term survival. Since patients with HAL seldom exhibit specific clinical manifestations, an accurate and timely diagnosis is challenging. Hence, the pathological characteristics of HAL may be crucial for its early diagnosis. In this study, we present a case of an old male patient with primary HAL.

2. Case report

We report a 70-year-old Chinese male patient with alcoholic intake over 30 years and smoking history of 60 cigarettes per day for 40 years. He sought medical consultation for productive cough and hemoptysis sputum. Chest CT scan revealed a mass (6.4 × 5.5 cm) in the left lower lobe of the lung. Mediastinal lymph nodes of the patient were slightly swollen (Fig. 1). An abdominal CT scan demonstrated that no definite focal lesion was observed in the liver, spleen, pancreas and gall bladder. Brain magnetic imaging revealed the occurrence of multiple small lacunes in the brain. No abnormal enhanced masses or nodules was found in the bilateral cerebral hemispheres, pons and cerebellum. Respiratory system tumor marker tests indicated that the levels of carcinoembryonic antigen (CEA) and CK19 were increased to 11.16 ng/ml and 7.01 ng/ml, respectively. It was noted that the total number of red blood cells (3.93 × 10↓) and the biochemical levels of ALT (54 U/L↑), AST (87 U/L↑) and γ-GT (990 U/L↑) were abnormal. These abnormalities may be due to chronic excessive alcohol consumption.

The patient underwent curative surgical resection on August 4, 2014. During thoracoscopic examination, an 8 × 5 cm mass was found in the left lower lobe of the lung, with adhesion to visceral pleura (Fig. 2). Moreover, the tumor was spread to a small part of

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Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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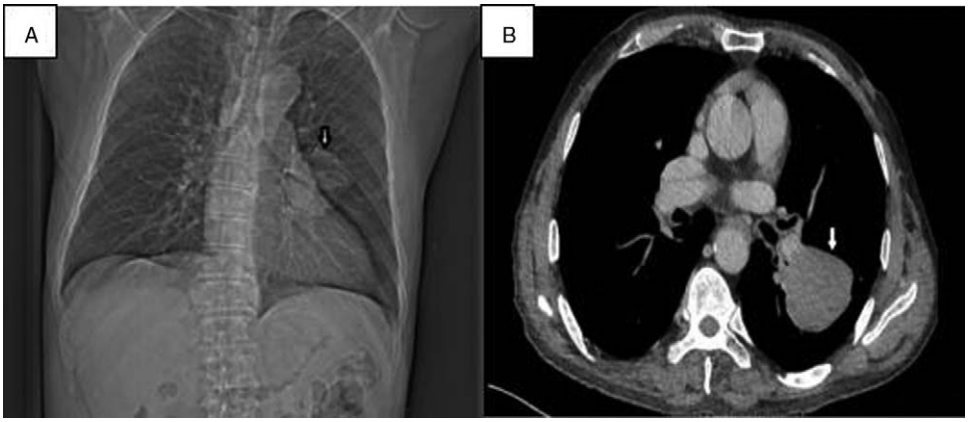

Figure 1. (A) Chest radiograph demonstrates a left lower lobe mass (arrow). (B) Chest computed tomography reveals a 6.4 cm mass (arrow) in the left lower lobe.

the left upper lobe. Therefore, a left pneumonectomy with radical lymph node dissection was performed. Macroscopic examination revealed that the tumor ($6 \times 6 \times 5.5$ cm) measured on the largest cut surface appeared as a solid gray-white node. Furthermore, visceral pleural invasion was observed in this patient.

Hematoxylin and eosin staining indicated a poorly differentiated carcinoma arranged in a sheet-like or trabecular growth pattern, with occasional tubular regions (Fig. 3). Extensive necrosis was noted in this patient. The tumor cells were large and polygonal, with abundant eosinophilic cytoplasm and centrally-located prominent nucleoli. Cytoplasmic bile plugs and periodic acid-Schiff-positive, diastase-resistant hyaline globules were found in this patient (Fig. 3). These morphological features were relatively similar to HCC. In addition, this case exhibited high mitotic counts (30–40 mitotic figures per 2 mm^2) and high proliferation index (Ki67 scores: 30%).

Immunohistochemical (IHC) analysis revealed that the neoplastic cells were strongly positive for HepoPar-1, CKpan, CK8/18, CK19 and MOC31 (anti-EpCAM), while focally positive for AFP and monoclonal CEA. CD34 staining demonstrated an intricate network of sinusoidal vessels surrounded the tumor cells. In contrast, Arg-1, SALL-4, CK5/6, CK7, CK14, CK20, syn, CD56, TTF-1, napsin A, P40, P63, P53, EGFR and ALK staining were considered negative were found to be negative by IHC staining (Fig. 3). Besides, the hilar lymph node was invaded (1/2). Taking into consideration the clinical, morphological and immunohistochemical features, this patient was diagnosed as HAL. Of note, his pathological staging was pT3N1M0.

Serum level of AFP was not measured prior to surgical operation. On the tenth postoperative day, the serum AFP level was detected as normal (2.07 IU/ml). This patient discharged on the twentieth day and refused further chemotherapy. Eighteen

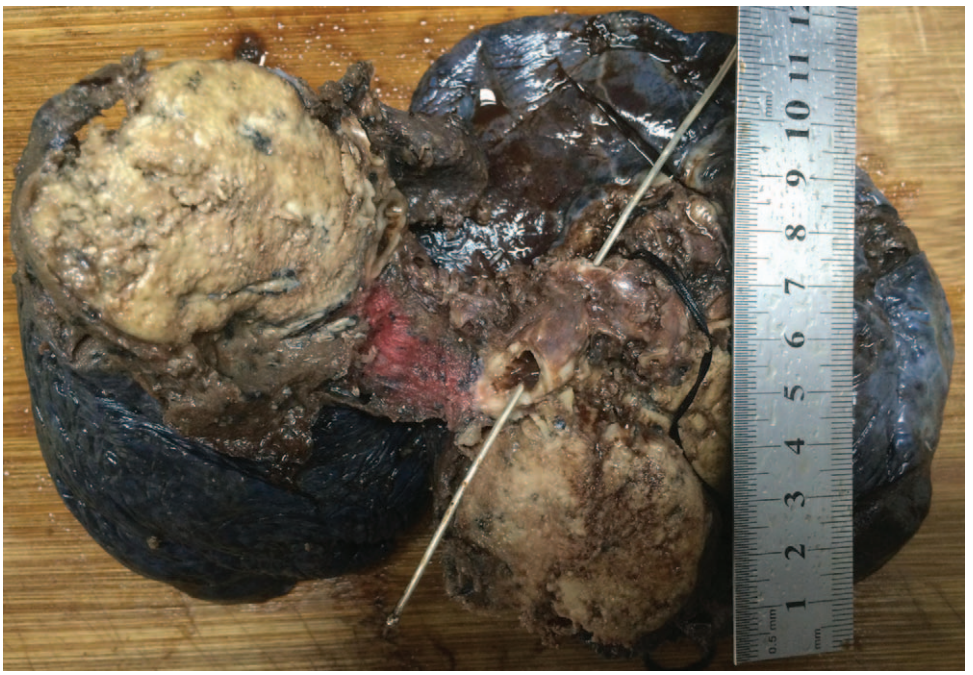

Figure 2. Left lower lobe mass ($6 \times 6 \times 5.5$ cm) appears as solid, white-grayish, firm tumor part surrounding the bronchi.

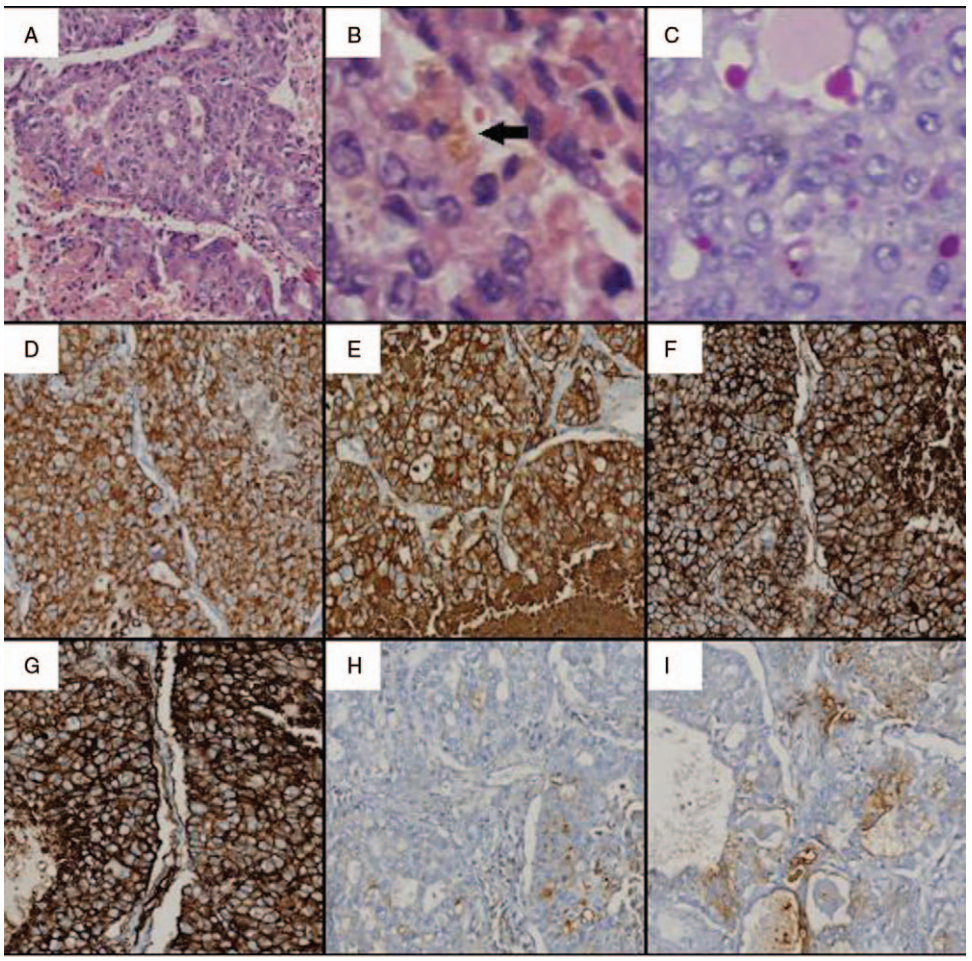

Figure 3. (A) Tumor cells are arranged in sheet-like or trabecular proliferation patterns, resembling HCC with focal necrosis. Hematoxylin and eosin (HE) staining, 100×. (B) Cytoplasmic bile plugs (arrow). HE staining, 200×. (C) Periodic acid-Schiff (PAS)-positive, diastase-resistant hyaline globules. PAS staining, 200×. (D–G) Immunohistochemistry reveals diffusely positive for HepPar-1, CK8, CK19, and MOC31. Immunohistochemical (IHC) staining, 100×. (H) Immunohistochemistry shows positive focal staining for AFP. IHC staining, 100×. (I) Localization of monoclonal CEA to the cytoplasm and cell membrane. IHC staining, 100×.

months after primary diagnosis, this patient died of multiple organ failure caused by distant metastases.

3. Discussion

HAC was first recognized as a gastric tumor in 1985 by Ishikura et al,[3] as defined by having an extremely high serum level of AFP and morphological features similar to HCC. This rare tumor can be found as a primary carcinoma in extrahepatic organs such as lung, ovary[4], pancreas[5], urinary bladder[6], ampulla of Vater[7], endometrium[8] and uterine cervix.[9] The most common site of HAC is gastric (63%), followed by ovaries (10%), lung (5%), gallbladder (4%), pancreas (4%) and uterus (4%).[2]

HAL was first described by Ishikura et al[10] in 1990. They studied 7 cases of AFP-producing lung carcinoma and diagnosed 5 of the 7 cases with HAC. Two criteria have been adopted by them for the diagnosis of HAL:

1. typical acinar or papillary adenocarcinoma; and
2. a component of carcinoma that resembles HCC and produces AFP.

However, later reports described HAL as a component of neuroendocrine carcinoma or signet-ring cells, instead of adenocarcinoma.[11,12] In patients without high AFP level, both morphology and immunophenotyping can assist the diagnosis of HAL.[13–16] In 2014, Haninger et al[17] have modified the Ishikura diagnostic criteria for HAL:

1. the tumor can be pure HAC or has a component of typical acinar or papillary adenocarcinoma, signet-ring cells or neuroendocrine carcinoma; and
2. AFP expression is not mandatory for diagnosis as long as other markers of hepatic differentiation are expressed.

The morphological features of HAL are remarkably similar to HCC. Since lung is the most common site for extrahepatic metastasis, the omission of metastatic HCC is clinically relevant. Computed tomography (CT) examination and immunostaining patterns may be particularly useful in this regard. CT can be used to detect the location of HAL tumor. However, if there are multiple tumors in different locations, it can be difficult to identify the primary tumor site. Haninger et al[17] have used a panel of antibodies to detect the immunohistochemical profiles of five patients with HAL and HCC. They found that all of them co-expressed APF, HepPar 1, CK8 and CK18, and exhibited positive cytoplasmic staining for TTF-1, but not CK14. Unlike HCC, HAL patients expressed only napsin A, monoclonal CEA,

Table 1

HAL cases summarized.

Year	Author	Gender-Age	Location	Size	Smoker	AFP level (ng/ml)	Stage	Treatment	Progression
1981	Yasunami[18]	Male-67	Left upper lobe	'Fist-sized'	Not given	19,000–160,000	pT3N2	XRT, Immuno tx (BCG)	Rib and vertebra metastases; Died 16 months after presentation
1981	Yokoyama[19]	Male-69	Right lower lobe	$11 \times 11 \times 7$	Not given	5050–88,000	pT3M1b	Not applicable	Died 2 months after presentation
1986	Miyake[20]	Male-40	Right upper lobe	$8 \times 9 \times 7$	Not given	3090	pT3M1b	Surg,	Died 14 months after presentation
1986	Miyake[20]	Male-55	Right upper lobe	5	Not given	2123	pT2aM1b	Surg,	Died 4 days after presentation
1987	Miyake[21]	Male-73	Left upper lobe	$5 \times 6 \times 5$	Not given	1039 preoperatively, normalized after lobectomy, did not increase upon relapse with brain metastases	pT2bM2	Surg, XRT	Mediastinal, LN, brain metastases; Died 18 months after presentation
1988	Saka[22]	Male-73	Right upper lobe	$3.9 \times 3 \times 3$	Not given	289 preoperatively, normalized after surgery	pT2N0M0	Surg	No progression 28 months after presentation
1992	Okunaka[23]	Male-49	Right upper lobe	$6 \times 5 \times 5$	Not given	9300, returned to normal post-operatively	eT3	Surg	No progression 11 months after presentation
1997	Nasu[24]	Male-63	Right upper lobe	$14 \times 13 \times 12$	Not given	14,000–100,000	cT4N2	Chemo	Lung, right adrenal, brain metastases; Died 11 months after presentation
1997	Amould[25]	Male-36	Left upper lobe	11	Yes	6090, dropped postoperatively, increased upon relapse with brain metastases	pT4N2	Chemo, Surg	Brain metastasis; Died 7 months after presentation
2000	Carlinfante[26]	Male-82	Left lower lobe	3.5	Yes	Not assayed	cT2aN0M0	Surg	No progression 7 years after presentation
2002	Hayashi[27]	Male-55	Right upper lobe	$5 \times 4.8 \times 6.5$	Yes	Not assayed before surgery, 89 on the 6th day after lobectomy, normalized on the 40th post-operative day	pT2bN0	Surg	No progression 32 months after presentation
2002	Hiroshima[11]	Male-71	Right lower lobe	$10.5 \times 8.5 \times 7$	Yes	9826, decreased after lobectomy	pT3N1M0	Surg, WBRT	Lung and brain metastases; Died 1 year after presentation
2003	Genova[28]	Male-71	Left upper lobe	7.7×6.4	Not given	Not assayed	pT3N0	Surg	No progression 24 months after presentation
2003	Terracciano[29]	Male-49	Left lower lobe	5	Not given	203,320	pT2b	Surg	Died 2 months after presentation
2003	Lino[30]	Male-63	Right upper lobe	2.8×2.5	Not given	Not assayed	cT1N0M0	Surg	No progression 5 months after presentation
2004	Oshiro[31]	Male-76	Right lower lobe	Not reported	Not given	Not assayed	cT2N0M0	Surg	Liver metastase; Died 18 months after presentation
2007	Wu[13]	Male-50	Right upper lobe	$6 \times 5 \times 5$	Yes	Normal	cT2N1M0	Surg	Alive with disease at 45 months
2007	Ivan[32]	Male-54	Left upper lobe	13×11	Yes	14,540	pT4N3M1	Chemo, XRT	Not reported
2008	Kishimoto[12]	Male-64	Left lower lobe	$7.5 \times 7 \times 4$	Not given	673, normalized after lobectomy	cT3N0M0	Surg	Not reported
2009	Kim[33]	Male-49	Left upper lobe	6	Not given	14,707	pT2bN1	Surg	Not reported
2010	Fornasa[14]	Female-68	Left upper lobe	$4.5 \times 4 \times 4$	No	Normal	pT2b	Chemo	Alive with disease at 15 months
2011	Papatsimpas[34]	Male-48	Right upper lobe	$20 \times 11 \times 8$	Not given	38,945–59,200	cT4	Chemo, XRT	Died 6 months after presentation
2012	Valentino[35]	Male-71	Right lower lobe	$1.8 \times 1.5 \times 1.5$	No	34,791	pT1N0M1	Chemo, XRT, Surg	Died 4 months after presentation
2012	Mokrim[36]	Male-52	Left upper lobe	$11.8 \times 12 \times 8$	Yes	5000	cT3N0M1	Palliative Chemo	Alive 6-7 months after presentation

(*continued*)

Table 1

(continued).

Year	Author	Gender-Age	Location	Size	Smoker	AFP level (ng/ml)	Stage	Treatment	Progression
2012	Khozin[15]	Female-56	Right anterior cardiophrenic angel; right middle lobe	5.5; 1.8	Yes	2	cT4	Chemo	Radiologic progression of lung disease 6 months after initiation of therapy
2013	Lin[37]	Male-66	Right upper lobe	$7.4 \times 6 \times 4.8$	Yes	8686	cT3N2M0	Surg, adjuvant chemo	Alive with disease at 15 months
2014	Che[38]	Male-66	Left upper lobe	$7.8 \times 7.9 \times 10$	Yes	6283	pT4N1M0	Chemo, XRT	Died 36 months after presentation
2014	Shaib[39]	Female-53	Right upper lob	$9.5 \times 9.0 \times 8.0$	Yes	37,810	pT3N0M0	Surg	No progression 4 years after presentation
2014	Haninger[17]	Male-51	Right upper lobe	4.2×3.7	Yes	Not assayed before surgery, 1.3 after lobectomy	cT2aN3M0	Chemo, XRT, Surg	Died 14 months after presentation
2014	Haninger[17]	Male-52	Right upper lobe	2.5	Yes	Not assayed	cT1bN0M1b	Surg,Chemo, XRT	Alive 37 months after presentation
2014	Haninger[17]	Male-64	Left upper lobe	3.2×2.2	Yes	Not assayed before surgery, 1.0 after lobectomy	cT2aN0M1b	Surg,Chemo, XRT	Died 10 months after presentation
2014	Haninger[17]	Female-54	Left upper lobe	1	Yes	Not assayed	cT1aN0M1b	Chemo, XRT, Surg	Alive 9 years after presentation
2014	Haninger[17]	Male-60	Right upper lobe	$11.2 \times 10.1 \times 8.5$	Yes	4410	cT3N2M1b	Chemo, XRT	Alive 1 months after presentation
2015	Gavrancic[40]	Male-64	Right upper lobe	3.8×2.9	Not given	181	cT2N2M1	Chemo, Sorafenib, XRT	Died 11 months after presentation
2016	Grossman[16]	Male-54	Right upper lobe/Paratracheal	4.1×5.1	Yes	2	pT4N0M1b	XRT	Died 4 months after presentation
2016	Motooka[41]	Male-69	Left segments 1+2	4.3	Yes	4497	cT2aN0M0	Surg, Chemo	No progression 51 months after presentation
2016	Sun[42]	Male-59	Right upper lobe	$4.5 \times 3.8 \times 3.5$	Yes	Not assayed before surgery, normal after lobectomy	pT2aN0M0	Surg	No progression 23 months after presentation
2016	Qian[43]	Male-79	Right parahilar	2.7×2.6	Yes	357–698	cT1cN0M0	Erlotinib	Not reported
2016	Wang[44]	Male-56	Right upper lobe	$4.0 \times 4.1 \times 4.8$	Not given	Not given	cT2N1M0	Not given	Not given
2017	Valle[45]	Male-61	Left lung	Not given	Not given	Not given	cT4	Chemo, Radiation therapy	Tonsil metastases; Died 55 months after presentation
2017	Li (current)	Male-70	Left lower lobe	$6 \times 6 \times 5.5$	Yes	Not assayed before surgery, normal after lobectomy	pT3N1M0	Surg	Died 18 months after presentation

EpCAM markers of HEA125 and MOC31, and a variety of cytokeratins such as CK5/6, CK7, CK19 and CK20. On the contrary, the panel of cytokeratins, napsin A and EpCAM markers are not expressed in HCC patients. Immunostaining reveal that the co-localization of CEA to the cytoplasm and cell membrane is found in 3 out of 5 HAL cases. Nevertheless, HCC is not stained by monoclonal CEA, but demonstrates a distinctive canalicular staining pattern with polyclonal CEA.

A systematic search in PUBMED was conducted to identify all HAC cases reported in the English literature prior to Dec 2016. The search was carried out using the search terms of "AFP producing tumor lung", "hepatoid carcinoma lung" and "hepatoid adenocarcinoma lung". The results of literature search and article selection were reviewed and verified by all authors in order to ensure data accuracy and appropriateness. After reviewing the literature, all cases with primary pulmonary hepatoid carcinoma are listed in Table 1.[11,44] A dramatic male predominance of 37/41 cases (90%) was found in this disease, and all of them, except one, were heavy smokers. Patients included in this study had a mean age of 60.5 years (range, 36–82 years). There is no characteristic imaging features of HAL. But in general, a chest radiograph and chest CT revealed a mass in the lung. It is probably that the mass shows heterogeneous enhancement on contrast chest CT images and intense FDG uptake on PET/CT images. The size of tumor was ranged from 1 to 20 cm in the largest dimension, with a mean size of 6.8 cm. Most cases (89%) were detected with a tumor size of greater than 3 cm, which located at the right upper lobe (44%). The majority of patients suffered from advanced stage disease and poor prognosis. In addition, metastases of the rib, vertebra, adrenal, brain, liver and tonsil were reported among HAL patients. Only few patients demonstrated long term disease-free survival, including a female patient with stage IV disease who is alive 9 years after diagnosis. These findings suggest that the clinical stage is the most significant prognostic factor for HAL, as similar to other types of non-small cell lung cancer. Pretreatment levels of AFP were markedly elevated in 22 out of the 26 detected patients. According to the modified diagnostic criteria of HAL, AFP expression is not mandatory for HAL diagnosis, provided that other markers of hepatic differentiation are expressed. However, an elevated serum AFP levels may indicate an increased risk of HAC among elderly male smokers with lung mass.

HAL is an extremely heterogeneous type of tumor, and thus no standard treatment is available at present. The common regimens for HAL patients are: surgical resection, chemotherapy and radiotherapy. A comprehensive review of all published cases has suggested that HAL patients diagnosed at early stage were associated with longer survival time after surgical treatment. For advanced stage patients, efforts continue in attempting radiotherapy and chemotherapy regimens. Gavarancic et al[39] have reported that a combination of sorafenib and platinum-based doublet chemotherapy is well-tolerated in AFP-producing, EGFR wild-type HAL patient. As a result, the patient with stage IV unresectable HAL demonstrated a long-term survival benefit after the proposed treatment.[39] Additionally, Valle et al[44] have described a 30 Gray (Gy) irradiation to achieve durable tumor control in HAL patients through intensity-modulated radiation therapy (IMRT). Such treatment has been proven effective for palliation of symptoms arising from metastatic HAL.[44]

Nonetheless, this study had several weaknesses, primarily the small sample size due to the rarity of HAL. Therefore, more cases should be concerned and recruited. Despite this limitation, we presented a new case of HAL and comprehensively summarized his clinical features, modified diagnostic criteria and treatments of the previously reported cases, in order to provide clinicians and pathologists with a more complete understanding of this rare tumor for avoiding misdiagnosis and mistreatment.

In summary, HAL is a rare tumor with male predilection and morphologically resembles metastatic HCC. Distinguishing it from metastatic HCC may require radiologic-morphologic-immunophenotypic correlation. AFP expression is not a requisite for the clinical diagnosis of HAL, but elevated AFP serum levels may indicate an increased risk of HAC among elderly male smokers with lung mass. Surgical resection appears to be the most effective treatment option for early stage HAL patients, which relies heavily on the histological diagnosis. Certain types of chemotherapy and radiotherapy can be effective in treating HAL. Further studies are needed to develop new treatments for this rare disease.

Author contributions

Data curation: Kun Yang, Qiuyao Li.
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Writing – original draft: Kun Yang, Qiuyao Li, Huifeng Jiang.
Writing – review & editing: Kun Yang, Qiuyao Li.
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