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.\textsuperscript{[1]} The primary sites of origin for HAC are lungs, with an occurrence rate of 5% among lung cancer cases.\textsuperscript{[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 11.16ng/ml and 7.01ng/ml, respectively. It was noted that the total number of red blood cells (3.93 × 10\textsuperscript{12}/L) and the biochemical levels of ALT (54U/L) and AST (87U/L) and γ-GT (990U/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...
the left upper lobe. Therefore, a left pneumonectomy with radical lymph node dissection was performed.Macroscopic examination revealed that the tumor (6 × 6 × 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 mm²) 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
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., 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, pancreas, urinary bladder, ampulla of Vater, endometrium and uterine cervix. The most common site of HAC is gastric (63%), followed by ovaries (10%), lung (5%), gallbladder (4%), pancreas (4%) and uterus (4%).

HAL was first described by Ishikura et al. 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. In patients without high AFP level, both morphology and immunophenotyping can assist the diagnosis of HAL. In 2014, Haninger et al. 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. 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 AFP, 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,

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×.
| 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) | Died 16 months after presentation |
| 1981 | Yokoyama [19] | Male-69 | Right lower lobe | 11 × 11 × 7 | Not given | 5050–88,000 | pT3M1b | Not applicable | Died 2 months after presentation |
| 1986 | Miyake [20] | Male-55 | Right upper lobe | 5 | Not given | 2123 | pT2aM1b | Surg | Died 4 days after presentation |
| 1986 | Miyake [20] | Male-73 | Left upper lobe | 5 × 6 × 5 | Not given | 1039 preoperatively, normalized after lobectomy, did not increase upon relapse with brain metastases | cT4N2 | Chemo | Died 11 months after presentation |
| 1988 | Saka [22] | Male-73 | Left upper lobe | 3.9 × 3 × 3 | Not given | 289 preoperatively, normalized after surgery | pT2N0M0 | Surg | No progression 28 months after presentation |
| 1989 | Okumura [23] | Male-49 | Right upper lobe | 6 × 5 × 5 | Not given | 9300, returned to normal postoperatively | eT3 | Surg | No progression 11 months after presentation |
| 1997 | Nasu [24] | Male-63 | Right upper lobe | 14 × 13 × 12 | Not given | 14,000–100,000 | cT4N2 | Chemo | Died 1 year after presentation |
| 1997 | Arnould [25] | Male-36 | Left upper lobe | 11 | Yes | 6690, dropped postoperatively, increased upon relapse with brain metastases | pT4N2 | Chemo, Surg | 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 × 4.8 × 6.5 | Yes | Not assayed before surgery, 89 on the 6th day after lobectomy, normalized on the 40th postoperative day | pT2N0 | Surg | No progression 32 months after presentation |
| 2002 | Hirashima [28] | Male-71 | Right lower lobe | 10.5 × 8.5 × 7 | Yes | 9626, decreased after lobectomy | pT3N1M0 | Surg, WBRT | Lung and brain metastases; Died 1 year after presentation |
| 2003 | Genova [29] | Male-71 | Left upper lobe | 7.7 × 6.4 | Not given | Not assayed | pT3N0 | Surg | No progression 24 months after presentation |
| 2003 | Terraciano [30] | Male-49 | Left lower lobe | 5 | Not given | 203,320 | pT2b | Surg | Died 2 months after presentation |
| 2003 | Iino [31] | Male-63 | Right upper lobe | 2.8 × 2.5 | Not given | Not assayed | cT1N0M0 | Surg | No progression 5 months after presentation |
| 2004 | Oshio [32] | Male-76 | Right lower lobe | Not reported | Not given | Not assayed | cT2N0M0 | Surg | Liver metastases; Died 18 months after presentation |
| 2008 | Wu [33] | Male-50 | Right upper lobe | 6 × 5 × 5 | Yes | Normal | cT2N1M0 | Surg | Alive with disease at 45 months |
| 2009 | Kishimoto [34] | Male-54 | Left upper lobe | 13 × 11 | Yes | 14,540 | pT4N3M1 | Chemo, XRT | Not reported |
| 2009 | Kishimoto [35] | Male-64 | Left lower lobe | 7.5 × 7 × 4 | Not given | 673, normalized after lobectomy | cT3N0M0 | Surg | Not reported |
| 2009 | Kim [36] | Male-49 | Left upper lobe | 6 | Not given | 13,407 | pT2M1 | Surg | Not reported |
| 2010 | Fornace [37] | Female-68 | Left upper lobe | 4.5 × 4.4 | No | Normal | pT2b | Chemo | Alive with disease at 15 months |
| 2011 | Papadopoulos [38] | Male-48 | Right upper lobe | 20 × 11 × 8 | Not given | 38,945–50,200 | cT4 | Chemo, XRT | Died 6 months after presentation |
| 2011 | Valenti [39] | Male-71 | Right lower lobe | 1.8 × 1.5 × 1.5 | No | 34,791 | pT1N0M1 | Chemo, XRT, Surg | Died 4 months after presentation |
| 2012 | Mokini [40] | Male-52 | Left upper lobe | 11.8 × 12 × 8 | Yes | 5000 | cT3N0M1 | Palliative Chemo | Alive 6-7 months after presentation |

(continued)
| Year | Author | Gender-Age | Location | Size | Smoker | AFP level (ng/ml) | Stage | Treatment | Progression |
|------|--------|------------|----------|------|--------|------------------|-------|-----------|-------------|
| 2012 | Khozin [15] | Female-56 | Right anterior cardiophrenic angle; 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 × 6 × 4.8 | Yes | 8680 | cT3N2M0 | Surg, adjuvant chemo | Alive with disease at 15 months |
| 2014 | Che [38] | Male-66 | Left upper lobe | 7.8 × 7.9 × 10 | Yes | 6283 | pT4N1M0 | Chemo, XRT | Died 36 months after presentation |
| 2014 | Shabt [39] | Female-53 | Right upper lobe | 9.5 × 9.0 × 8.0 | Yes | 37,810 | pT3N0M0 | Surg | No progression 4 years after presentation |
| 2014 | Haninger [17] | Male-51 | Right upper lobe | 42 × 3.7 | Yes | Not assayed before surgery, 1.3 after lobectomy | cT2aN0M0 | 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 × 10.1 × 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 [41] | Male-54 | Right upper lobe/Parastrachal | 4.1 × 5.1 | Not given | 2 | pT4N0M1b | XRT | Died 4 months after presentation |
| 2016 | Motooka [42] | 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 × 3.8 × 3.5 | Yes | Not assayed before surgery, normal after lobectomy | pT2aN0M0 | Surg | No progression 23 months after presentation |
| 2016 | Qin [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 × 4.1 × 4.8 | Not given | Not given | cT2N1M0 | NOT GIVEN | Tonsil metastases; Died 55 months after presentation |
| 2017 | Valle [45] | Male-61 | Left lung | Not given | Not given | Not given | cT4 | Chemo, Radiation therapy | Died 18 months after presentation |
| 2017 | Li (current) [15] | Male-70 | Left lower lobe | 6 × 6 × 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 reveals 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 HAL 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. 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 60.3 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, Vallee 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 some 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

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